Total Syntheses of Fastigiatine and the Hibarimicin Aglycons

Total Syntheses of Fastigiatine and the Hibarimicin Aglycons

A dissertation presented

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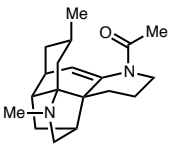
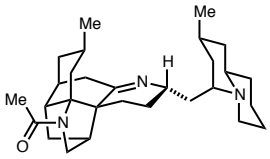
Abstract

Part one of this two-part thesis describes my efforts toward the total syntheses of the complex polycyclic alkaloids (–)-himeradine A and (+)-fastigiatine, which are members of the *Lycopodium* family of natural products. A cascade reaction sequence featuring a biosynthesis-inspired transannular Mannich reaction was planned to construct the strained and densely functionalized pentacyclic cores of the molecules from acyclic starting materials. After difficulties were encountered in a first-generation synthesis plan toward (–)-himeradine A, a second-generation synthesis plan was eventually successful in accomplishing the first total synthesis of (+)-fastigiatine via a formal [3+3]-cycloaddition reaction and a retro-aldol tandem transannular Mannich reaction sequence.

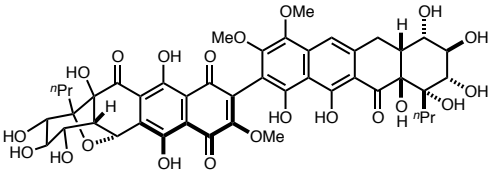
In part two of this thesis, syntheses of the hibarimicin aglycons, including HMP-Y1, atrop-HMP-Y1, hibarimicinone, atrop-hibarimicinone, and HMP-P1, are reported. These natural products are amongst the largest and most complex type-II polyketides isolated. A novel benzylic fluoride Michael–Claisen reaction sequence was developed to construct the complete carbon skeleton of HMP-Y1 and atrop-HMP-Y1 via a symmetrical bidirectional double annulation reaction. Through efforts to convert HMP-Y1 derivatives to hibarimicinone and HMP-P1, a biomimetic mono-oxidation to desymmetrize protected HMP-Y1 was realized. A bidirectional unsymmetrical double annulation and biomimetic etherification were developed to construct the polycyclic and highly-oxidized skeleton of hibarimicinone, atrop-hibarimicinone, and HMP-P1. Lastly, a pH-dependent rotational barrier about the C2–C2' bond of hibarimicinone was discovered, which provides valuable information for achieving the syntheses of the glycosylated congeners of hibarimicinone.



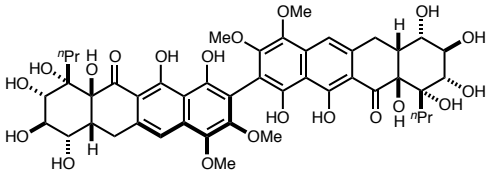
(+)-fastigiatine (**37**)



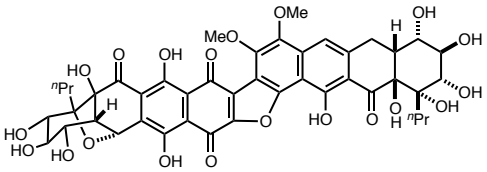
(–)-himeradine A (**38**)



hibarimicinone (**6**)



HMP-Y1 (**8**)



HMP-P1 (**10**)

Table of Contents

Acknowledgements

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I would like to thank my family for their guidance and support throughout my life and graduate school years. I've come a long way since calling you my freshman year, Mom, depressed that I was "failing" intro organic chemistry, and that transformation wouldn't have been possible without all of your love. Lastly, I would like to thank my lab mate, wife, and best friend, Amy Lee, for her advice, love, and caring support throughout graduate school. Who I am now and this thesis dissertation wouldn't have been possible without you, and I wanted to let you know how much I deeply appreciate that. I look forward to our years to come.

List of Abbreviations

)))	sonication
Å	angstrom
A(1,3)	1,3-allylic strain
Ac	acetyl
a*R*	axial rectus (Cahn–Ingold–Prelog system)
a*S*	axial sinister (Cahn–Ingold–Prelog system)
atrop	atropisomer
BBN	9-borobicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
BTSE	1,2-bis(trimethylsiloxy)ethane
Bu	butyl
Bz	benzoyl
c	concentration (g/100 mL)
° C	degree celsius
CAN	cerium(IV) ammonium nitrate
cat.	catalytic
Cbz	carbobenzyloxy
CD	circular dichroism
cis	*L.*, on the same side
COSY	correlation spectroscopy
Cp	cyclopentadienyl
cr	crown
CSA	camphorsulfonic acid
D	dimensional
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
δ	chemical shift
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	*Ger.,* entgegen
ee	enantiomeric excess
endo	*Gr.,* within
ent	enantiomer
Eq.	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
exo	*Gk.,* external
FABMS	fast atom bombardment mass spectrometry
FPT	freeze-pump-thaw
FTIR	Fourier transform infrared
g	gram
g	gauche
Grubbs I	Grubbs first-generation catalyst
h	hour
HMBC	heteronuclear multiple bond correlaton

HMDS	hexamethyldisilazane
HMQC	hetereonuclear multiple quantum coherence
HPLC	High-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	2-iodoxybenzoic acid
Imid	imidazole
INADEQUATE	incredible natural abundance double quantum transfer experiment
IR	infrared
J	coupling constant (in Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tetramethylipiperidide
2,6-lut	2,6-lutidine
M	molar (mols/liter)
µ	micro
µm	micron
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
min	minimize
mL	milliliter
mmol	millimole
mol	mole

MOM	methoxymethylether
MoOPh	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
MPTA	methoxy(trifluoromethyl)phenylacetic acid
MS	mass spectrometry
MsCl	methanesulfonyl chloride
NBS	*N*-bromosuccinimide
NIH3T3	National Institute of Health 3-day transfer, inoculum 3×10^5 cells
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	2-nitrobenzenesulfonyl
NsCl	2-nitrobenzenesulfonyl chloride
Ox.	oxidation
OTf	trifluoromethanesulfonate
P	protecting group
pent	pentane
pH	hydrogen ion concentration
Ph	phenyl
Phth	phthalimide
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Piv	pivoloyl
pKa	acid dissociation constant
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonic acid
^{n}Pr	*n*-propyl
PTLC	preparatory thin-layer chromatography
Py	pyridine
R	general substituent

R	rectus (Cahn–Ingold–Prelog system)
R_f	retention factor
RT	room temperature
RXN	reaction
S	general sugar substituent
S	sinister (Cahn–Ingold–Prelog system)
sec	seconds
stabase	1,4-(1,1,4,4-tetramethylsilylethylidene)
taut.	tautomerization
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSE	2-trimethylsilylethyl
TOCSY	total correlated spectroscopy
trans	*L.*, across
trig	trigonal
TsCl	*p*-toluenesulfonyl chloride
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
vis	visible
X	general substituent
Z	*Ger.*, zusammen

I. Total Synthesis of (+)-Fastigiatine

Chapter 1

Introduction to the *Lycopodium* Alkaloids

Introduction

The *Lycopodium* alkaloids are a diverse family of complex natural products isolated from the *Lycopodium* club mosses. The first *Lycopodium* alkaloid to be studied and isolated was lycopodine (**1**, Figure 1.1), which was separated by Bödeker in 1881[1] from *Lycopodium complanatum*. Since then, over 250 *Lycopodium* alkaloids have been identified and characterized to date, and are the subject of active biomedical and synthetic organic research.[2]

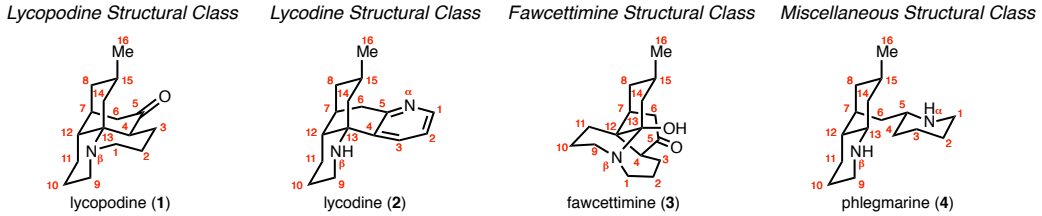

Figure 1.1 Representative *Lycopodium* alkaloids.

The *Lycopodium* alkaloids have been broadly classified into four related structural classes: the lycopodine class, the lycodine class, the fawcettimine class, and the miscellaneous class.[2c] Representative members of each class are depicted in Figure 1.1, where the positional numbering system depicted is in accordance with Conroy's original biosynthesis hypothesis.[3] Although Conroy's proposed skeletal connections have been generally corroborated, ^{14}C- and ^{13}C-feeding studies have led to a revised biosynthesis of the *Lycopodium* alkaloids.[4] Initially, lysine is decarboxylated and oxidatively cyclized to form Δ^1-piperideine (**7**, Figure 1.2). **7** is then proposed to undergo a Mannich

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[1] Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363–367.

[2] For reviews of the *Lycopodium* alkaloids, see: (a) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York; 2005, Vol. 61, pp 1–57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (c) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, pp 233–266.

[3] Conroy, H. *Tetrahedron Lett.* **1960**, *1*, 34–37.

[4] (a) Hemscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1996**, *118,* 1799–1800; (b) Hemscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1993**, *115,* 3020–3021, and references therein.

reaction with 3-oxoglutaric acid, which after subsequent decarboxylation would afford pelleterine (**9**). **9**, or an oxidized derivative, could then be dimerized via an intermolecular aldol reaction to yield dimer **10**. Subsequent oxidation and an intramolecular aldol reaction would then form the C7–C12 bond to yield the phlegmarine carbon skeleton **12**. **12** is poised to undergo an intramolecular Mannich reaction to establish the C4–C13 bond to construct tetracycle **13**, which forms the basic carbon skeleton of the lycodine structural class. Further hydrolysis of the C5–Nα imine of **13**, followed by deamination and formation of the C1–Nβ bond, is then proposed to lead to the lycopodine structural class. Oxidation of **1** at C12 would yield lycodoline (**14**), which upon migration of C4 from C13 to C12 is proposed to yield the fawcettimine structural class.[5] Each structural class can then undergo further oxidation and rearrangement, ultimately leading to the large and diverse *Lycopodium* alkaloid family of natural products.

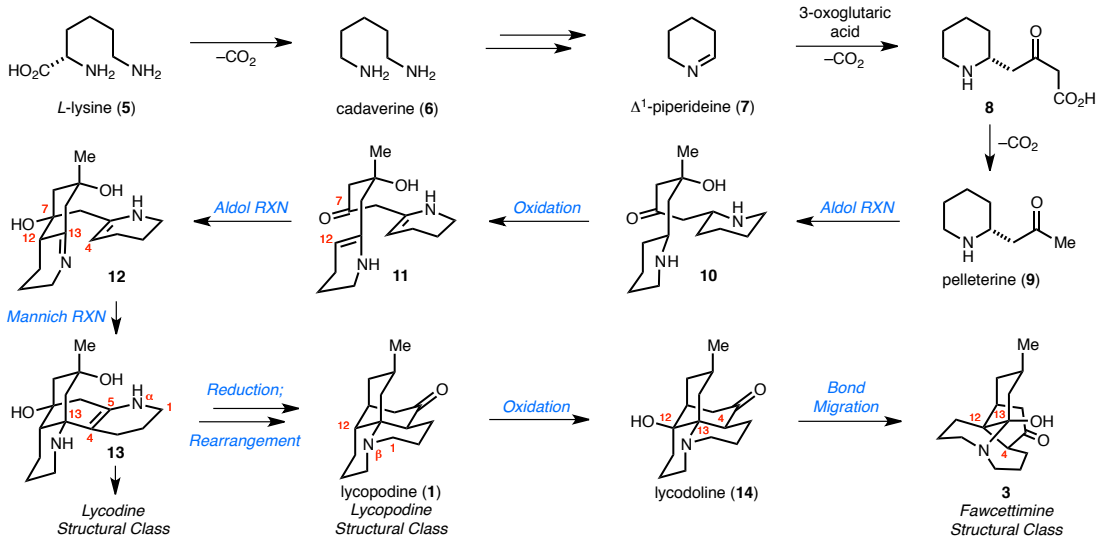

Figure 1.2 Proposed biosynthesis of the *Lycopodium* alkaloids.

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[5] Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1983; Chapter 5.

Selected Total Syntheses of Related *Lycopodium* Alkaloids

The *Lycopodium* alkaloids have a longstanding and rich history in organic synthesis. Since Stork's[6] and Ayer's[7] inaugural syntheses of lycopodine (**1**) in 1968, these natural products have continued to attract interest from the organic synthesis community due to their complex polycyclic architecture and diverse biological activities. In this section, four selected total syntheses of the *Lycopodium* alkaloids will be briefly discussed to provide context and background for chapter two.

Our discussion begins with the classic synthesis of (±)-lycopodine (**1**) by Stork and coworkers. Their synthesis commenced with the 1,4-conjugate addition of the organocuprate derived from methylmagnesium iodide and copper(I) chloride to 2-cyclohexenone **15** to afford cyclohexanone **16** as a single diastereomer (Scheme 1.1).[8] Treatment of **16** with pyrrolidine and *p*-toluenesulfonic acid led to the formation of the corresponding Stork pyrrolidinenamine, which upon exposure to acrylamide led to two regioisomeric quinolones. Fortunately, the desired quinolone **17** could be readily separated and carried forward. Next, Stork anticipated that protonation of **17** with acid would lead to formation of acyliminum ions **18** and **19**, which would be trapped in situ with the pendant methoxybenzyl group via an intramolecular Friedel–Crafts reaction to form the C4–C13 bond. Two epimeric products at C12, tetracycles **20** and **21**, are potentially accessible from this reaction sequence given that the initial protonation of **17** is either unselective or reversible. However, Stork predicted that if the protonation of enamide **17** is reversible and faster than the subsequent Friedel–Crafts alkylation, then only the desired epimer **20** would be formed via acyliminium ion **19** due to the unfavorable conformation needed for acyliminium ion **18** to react. Indeed, this application of the

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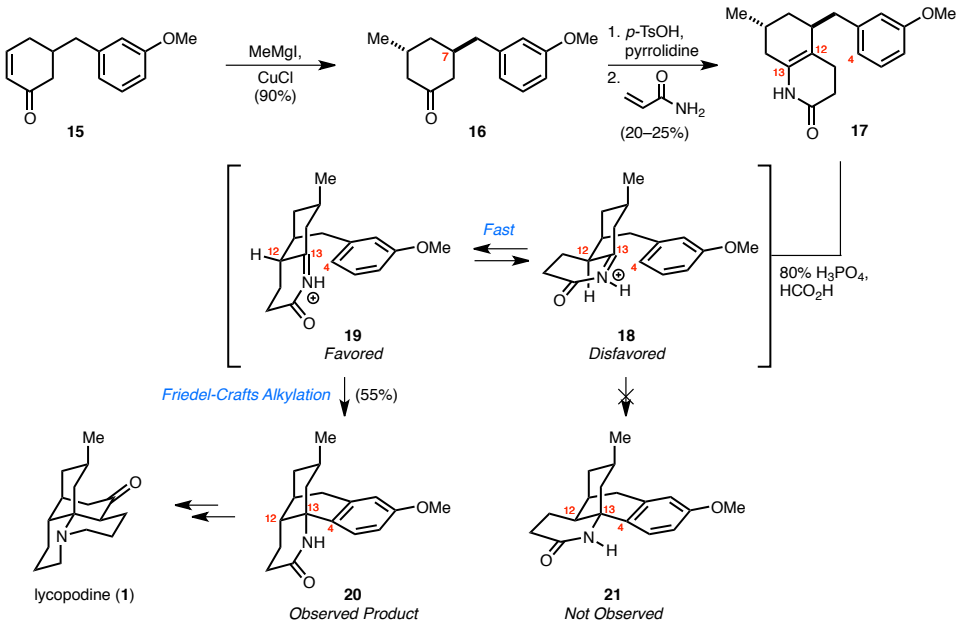
[6] Stork, G.; Kretchmer, R. H.; Schlessinger, J. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648.

[7] Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1648–1650.

[8] The high *anti*-diastereoselectivity of this transformation can be rationalized by stereoelectronically favored axial attack of the nucleophile onto a half-chair conformation of **15** that is anchored by the pseudo-equatorial C7-substituent. This *anti*-diastereoselectivity observed in additions to 5-substituted 2-cyclohexenones is quite general and is exploited in numerous syntheses of varying *Lycopodium* alkaloids (vide infra). See: Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, *12*, 1269–1272.

Curtin-Hammett principle proved to be correct, as desired epimer **20** was the only product observed aside from the *o*-cyclization isomer. Stork and coworkers completed the synthesis of (±)-lycopodine (**1**) from **20**, accomplishing a pioneering achievement in natural product total synthesis.



Scheme 1.1 Highlights from Stork's total synthesis of (±)-lycopodine (**1**).

A decade later, Heathcock and coworkers reported another synthesis of (±)-lycopodine (**1**).[9] Their synthesis began with the 1,4-conjugate addition of the lithium anion of *N*,*N*-dimethylhydrazone **23** to cyclohexenone **22**, to yield cyclohexanone **24** after hydrazone hydrolysis (Scheme 1.2). The initial 1,4-conjugate addition occurred exclusively *anti* to the C16-methyl group,[8] but the subsequent protonation of the resultant copper enolate was unselective and yielded a ~1:1 mixture of C12-epimers. This mixture of C12-epimers would later prove inconsequential due to a Curtin-Hammett kinetic situation analogous to what Stork had observed previously (vide infra). Global carbonyl protection and reduction of the nitrile led to primary amine **25**. Exposure of **25** to hydrochloric acid

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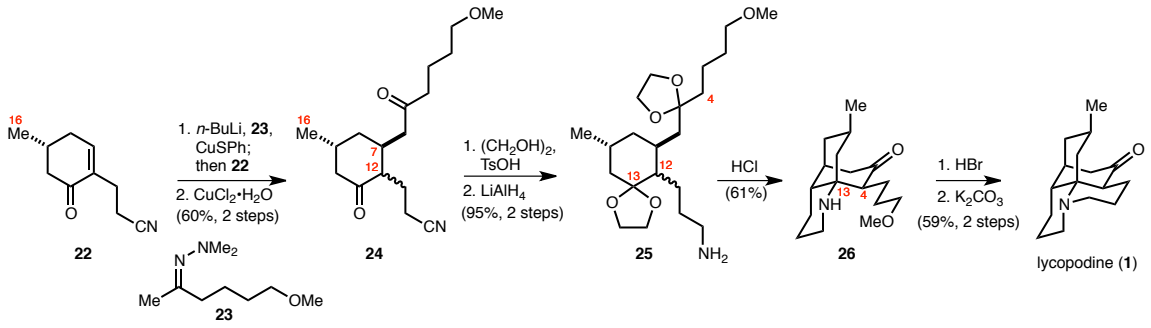
[9] (a) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1978**, *100*, 8036–8037; (b) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068.

triggered a cascade of reactions involving: (1) global ketal deprotection, (2) iminium ion formation, and (3) an intramolecular Mannich reaction to form the C4–C13 bond to yield tricycle **26** as a single diastereomer, despite the initial mixture of C12-epimers. Heathcock rationalized that the C12-epimers of the intermediate C13-iminium ion can rapidly interconvert via the Nβ–C13–C12 enamine tautomer but that only one C12-epimer can favorably cyclize via the intramolecular Mannich reaction, an argument very similar to that put forth by Stork.[6] (±)-Lycopodine (**1**) was then completed in two straightforward steps from **26**. The Heathcock synthesis of (±)-lycopodine (**1**) proved to be more efficient than Stork's prior synthesis, since the use of a Mannich reaction rather than a Friedel–Crafts alkylation to form the C4–C13 obviated further downstream manipulations. Nonetheless, the synthesis relied on a similar set of bond disconnections that Stork had pioneered earlier.

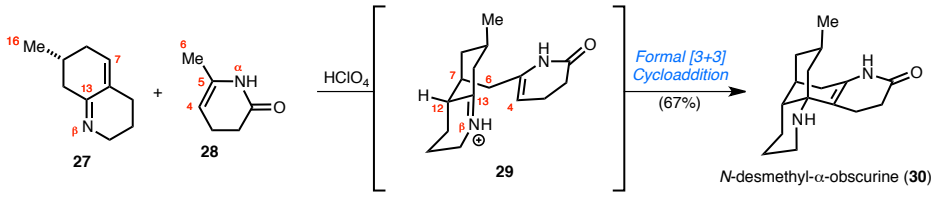


Scheme 1.2 Heathcock's synthesis of (±)-lycopodine (**1**).

Schumann and coworkers accomplished an elegant synthesis of (±)-*N*-desmethyl-α-obscurine (**30**) that employed a similar set of bond formations as Heathcock's synthesis of lycopodine but executed as a single cascade reaction (Scheme 1.3).[10] Heating α,β-unsaturated imine **27** with enamide **28** in the presence of perchloric acid led to a cascade of tandem reactions involving: (1)

[10] Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1983**, 220–225.

tautomerization of **28** to the exocyclic Nα–C5–C6 enamide,[11] (2) diastereoselective 1,4-conjugate addition of the exocyclic enamide to **27** *anti* to the C16-methyl group, (3) subsequent protonation of the resultant Nβ–C13–C12 enamine to yield iminium ion **29**, and (4) an intramolecular Mannich reaction to form the C4–C13 bond, affording **30**. Again, only one C12-epimer of **30** was observed for an analogous Curtin-Hammett kinetic argument as described earlier. This one-pot transformation constitutes a formal [3+3]-cycloaddition, similar variants of which have been developed and employed by others in complex molecule synthesis.[12]



Scheme 1.3 Schumann's synthesis of *N*-desmethyl-α-obscurine (**30**).

To conclude this chapter, key transformations from the more recent syntheses of the miscellaneous group *Lycopodium* alkaloid (+)-lyconadin A (**31**) and (–)-lyconadin B (**32**) by Smith and Beshore will be discussed (Scheme 1.4).[13] The lyconadins are more unusual members of the *Lycopodium* alkaloids in that they possess an additional C4–C10 linkage, which forms a 7-membered ring. In the key step of the Smith synthesis, treatment of ketoaldehyde **33** with hydrochloric acid led to a cascade of tandem reactions involving: (1) Robinson annulation to form cyclohexenone **34**, (2) stereoselective 7-*endo-trig* intramolecular 1,4-conjugate addition to form the C6–C7 bond, and (3)

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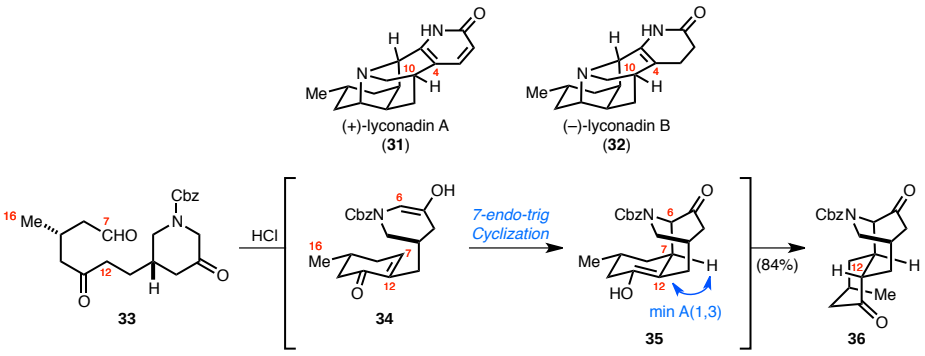
[11] Sarpong and Fischer later demonstrated that **28** may convert to the open-chain carboxamide methyl ketone with perchloric acid, and that this intermediate then enolizes and undergoes the formal [3+3]-cycloaddition. See Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927.

[12] For other examples of formal [3+3]-cycloadditions see: (a) Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008,** *64*, 883–893, and references therein; (b) Movassaghi, M.; Chen, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 565–568.

[13] (a) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149; (b) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.

protonation of the resultant enol **35** to afford tricycle **36** as a single diastereomer in 84% overall yield. As reminiscent of before, the C16-methyl group controlled the stereoselective formation of the C7-stereocenter by enforcing a pseudo-axial 1,4-conjugate addition reaction, except this time in the context of an intramolecular cyclization. The authors further argue that pseudo-equatorial attack onto cyclohexenone **34** is precluded due to developing 1,3-allylic strain between the C7- and C12-substituents in the transition state, rendering the process highly diastereoselective.[14] Unfortunately, the protonation at C12 was completely selective for the undesired epimer, and could not be directly epimerized under a variety of conditions. This is interesting since a Curtin-Hammett kinetic situation allowed the three previously discussed syntheses to obtain the desired C12-stereochemistry exclusively, suggesting that the unique structure of **35** is responsible for the observed selectivity.



Scheme 1.4 Highlights from Smith's syntheses of (+)-lyconadin A (**31**) and (–)-lyconadin B (**32**).

Together, these synthetic studies demonstrate the utility of the C16-methyl group for the stereoselective introduction of the C6–C7 bond, the facile ability to form the crucial C4–C13 bond via an intramolecular addition of a π-nucleophile to either an acyliminium or iminium ion, and how in such a reaction the initial C12-stereocenter is inconsequential due to a Curtin-Hammett kinetic situation. It is perhaps not surprising how facile and stereoselective the iminium ion mediated C4–

[14] This argument is most likely operative in the aforementioned syntheses developed by Heathcock and Schumann, which also contain substituents at C12 during the conjugate addition reaction.

C13 bond formation sequence is, since the bonds constructed mirror those formed during the proposed biosynthesis of the *Lycopodium* alkaloids. The above aspects of the aforementioned total syntheses heavily influenced the work described in the following chapter. These four selected syntheses are just a very small sample of the numerous syntheses of the *Lycopodium* alkaloids, which continue to be a rich family of targets for organic synthesis.

I. Total Synthesis of (+)-Fastigiatine

Chapter 2

Progress Toward a Total Synthesis of (–)-Himeradine A and the Total Synthesis of (+)-Fastigiatine

Introduction

A small subset of the *Lycopodium* alkaloids contains a pentacyclic core structure (Figure 2.1). Among these, (+)-fastigiatine (**37**)[15] and (–)-himeradine A (**38**)[16] belong to the lycodine structural class. Both molecules have an unprecedented pentacyclic core with a C4–C10 bond (highlighted in red), in contrast to lycodine (**2**). The additional strained C4–C10 linkage adds considerable complexity to these molecules, creating a densely functionalized pyrrolidine ring and an array of five contiguous stereocenters, which includes two vicinal all-substituted carbons. Himeradine A (**38**) contains an additional quinolizidine moiety appended to the pentacyclic core via a methylene linker.

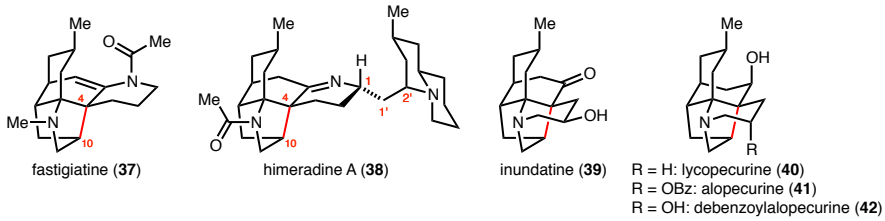


Figure 2.1 *Lycopodium* alkaloids containing a pentacyclic core with a C4–C10 bond.

The relative stereochemistry of fastigiatine (**37**) was unambiguously determined by X-ray crystallography.[15] In contrast, the structure and relative stereochemistry of each individual polycyclic subunit of **38** were only assigned on the basis of ^{1}H, ^{13}C, COSY, HMQC, HMBC, and NOESY NMR experiments as well as IR and FABMS/MS data.[16] Due to the relative isolation of the pentacyclic core and quinolizidine moiety, the relative stereochemistry between them remains ambiguous. However, the large vicinal coupling constants observed between C1' with C1 and C2', respectively, suggest that the relative conformation between the two subunits is rigidly locked. A Monte Carlo simulation followed by minimization was consistent with the NOESY data and coupling constants observed, leading the authors to propose that himeradine A (**38**) has the structure depicted in Figure 2.1.[16]

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[15] For isolation, see: (a) Gerard, R. V.; MacLean, D. B.; Fagianni, R.; Lock, C. J. *Can. J. Chem.* **1986**, *64*, 943–949; (b) Gerard, R.V.; MacLean D. B. *Phytochemistry* **1986**, *25*, 1143–1150.

[16] For isolation, see: Morita, H.; Hirasawa, Y.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 4563–4566.

The biosynthesis of the pentacyclic core of fastigiatine (**37**) and himeradine A (**38**), as proposed by MacLean,[15a] is shown in Figure 2.2 (top left to right). It was proposed that the lycodane skeleton **44** is first oxidatively functionalized at C10 to yield tetracycle **45**. Next, the pentacyclic core **46** could be derived from **45** by an enamine S_N2 cyclization to form the key C4–C10 bond. While plausible, the efficiency of the predicted alkylation reaction required to form **46** seems unfavorable, requiring **45** to adopt a strained boat-like conformation in order to achieve proper orbital overlap with a rather unactivated electrophile.

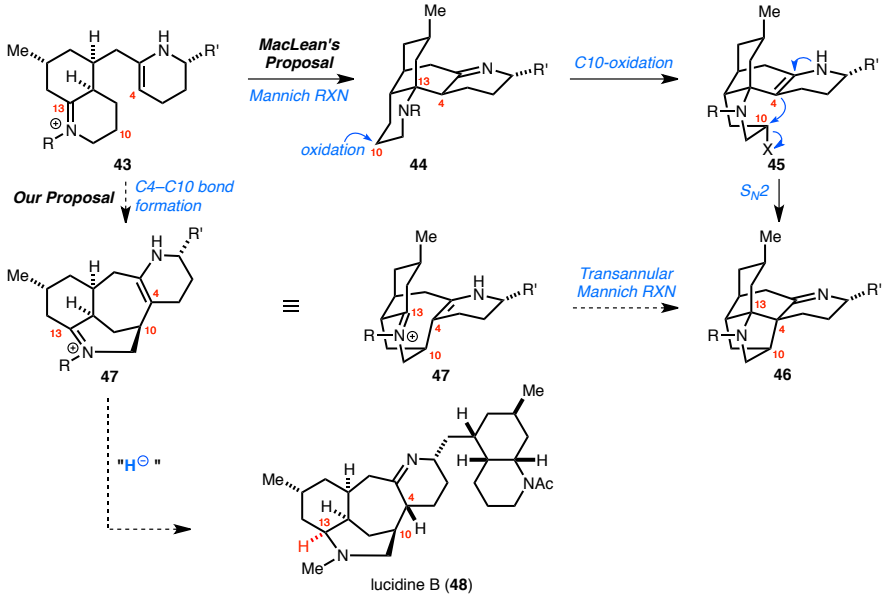

Figure 2.2 Proposed biosynthesis of the pentacyclic core of fastigiatine (**37**) and himeradine A (**38**).

Due to these considerations, we proposed an alternative biosynthesis shown in Figure 2.2 (top left and down). As detailed in chapter one in Figure 1.2, phelgmarine type skeleton **43** is the proposed precursor to the lycodine structural class via an intramolecular Mannich reaction to form the C4–C13 bond (i.e., **43** → **44**).[4,5] However, it is also possible that the C4–C10 bond of **37** and **38** is installed first at this stage to yield tetracycle **47**, prior to formation of the C4–C13 bond. This could also potentially take place via an intramolecular enamine S_N2 reaction of an oxidatively functionalized derivative of **43** at C10; however, the conformation of **43** needed for such a reaction to occur is less

strained than that needed for **45**. Tetracycle **47**, suggestively redrawn in a 3D-perspective, is next poised to undergo an intramolecular transannular Mannich reaction to form the core of fastigiatine (**37**) and himeradine A (**38**), in close analogy to the canonical Mannich reaction proposed in the *Lycopodium* alkaloid biosynthesis. Alternatively, intermediate **47** could be intercepted via reduction of the C13-iminium ion to give the core structure of lucidine B (**48**), a *Lycopodium* alkaloid isolated alongside himeradine A (**38**) from *Lycopodium chinense*.[16] Several other *Lycopodium* alkaloids possess structures containing a C4–C10 bond, such as the lyconadins,[13] and our alternative proposed biosynthesis could clearly explain their common origin with and divergence from the pentacyclic *Lycopodium* alkaloids. If the C4–C10 bond of lucidine B (**38**) and related alkaloids were to be generated via the originally proposed biosynthesis of fastigiatine (**37**) and himeradine A (**38**), this would necessitate a retro-Mannich reaction of core **46** to **47**, which would then be intercepted via a hydride equivalent. While this scenario is possible, we believe that our alternative proposed biosynthesis is equally plausible.

Given the structural complexity of the unprecedented pentacyclic core structure of fastigiatine (**37**) and himeradine A (**38**) as well as the biosynthetic questions surrounding their origin, I embarked on the total syntheses of these two molecules. Specifically, we wished to address whether a transannular Mannich reaction could be employed to synthesize these two molecules and thus test the feasibility of our proposed biosynthetic hypothesis. Prior to our published efforts[17] and the work described herein, no other synthetic studies toward **37** or **38** had been published.

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[17] Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595.

First-Generation Synthesis Plan

Our initial synthesis plan was designed to target himeradine A (**38**), with the plan that such a strategy could later be adapted to a synthesis of fastigiatine (**37**). In the interest of accomplishing a convergent synthesis, we proposed that the pentacyclic core **46** could be linked with quinolizidine **49** via a late-stage coupling reaction (Scheme 2.1). At this stage of planning, the coupling reaction was considered flexible, as we imagined that numerous strategies were possible. Next, as previously mentioned, we specifically wanted to address whether the pentacyclic core **46** could be constructed from tetracycle **47** via a transannular Mannich reaction to form the C4–C13 bond. Furthermore, we envisioned that **47** could be disassembled to linear precursor **51** via a cascade sequence of reactions. Briefly, this sequence of reactions would involve: (1) Robinson annulation to generate 2-cyclohexenone **50**,[18] (2) condensation of Nα and Nβ with the C5- and C13-carbonyls, respectively, and (3) subsequent intramolecular 1,4-conjugate addition to form the C6–C7 bond. At this point, numerous permutations of the aforementioned bond-forming events were potentially possible; however, we considered the specific order flexible and perhaps programmable through the use of different protecting group schemes. A more detailed analysis of specific cascade scenarios will be discussed (vide infra). **51** could arise via a coupling between "western" fragment **52** and "eastern" fragment **53**. Alternatively, the 2-cyclohexenone of **50** could be introduced as one complete subunit by coupling 2-cyclohexenone anion equivalent **54** with **52** directly. After the appropriate functional group manipulations, we imagined that **52** could be efficiently constructed by a convergent three-component coupling involving nucleophilic opening of cyclopropane **55**[19] with sodium azide and alkylation of the resultant dicarbonyl anion intermediate with iodide **56**.

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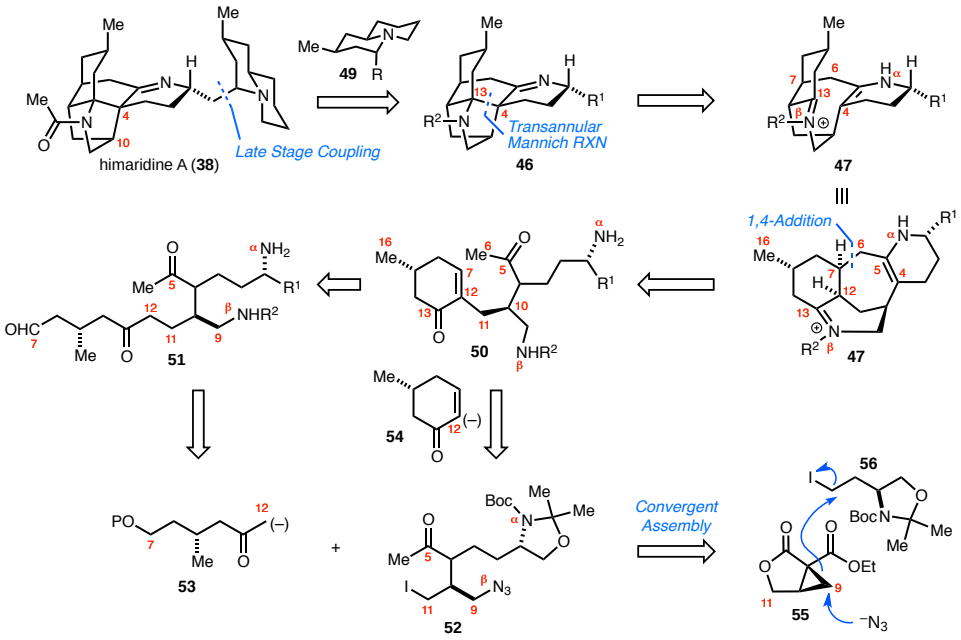
[18] The Nβ–C13–C12-enamine could also be employed to facilitate the Robinson annulation to directly construct the desired α,β-unsaturated imine.

[19] For a review on electrophilic cyclopropanes, see: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72.

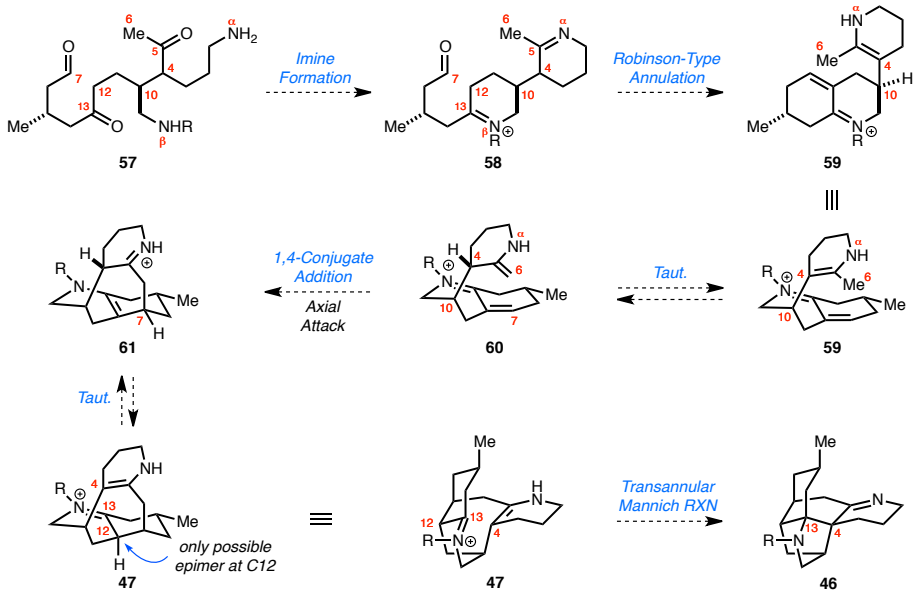


Scheme 2.1 First-generation retrosynthesis of himeradine A (**38**).

Several features concerning the chemo- and stereoselectivity of the proposed cascade to construct **46** deserve comment. We planned for two likely scenarios or sequence of events that are described in Scheme 2.2 and Scheme 2.3, which we could hopefully execute through the judicious choice of nitrogen protecting groups. In Scheme 2.2, we envisioned that condensation of Nα and Nβ with the C5- and C13-carbonyls in **57** would precede any carbon-carbon bond forming event to give **58**. While the presence of two amino groups and three carbonyls allows for many possible imine products, the only plausible bis-condensation product is **58**. Condensation of Nβ with the C5-carbonyl is the only other plausible unproductive reaction, but we envisioned that this process would be competitive with Nα so long as the process was reversible.[20] If necessary, orthogonal nitrogen protecting groups could possibly be employed to control the condensation reactions. Next the Nβ–C13–C12-enamine can engage in a Robinson-type annulation with the C7-aldehyde to give α,β-

[20] This would turn out to be a very naïve hypothesis.

unsaturated iminium ion **59**.[21] Next, the Nα–C5–C4-endocyclic enamine of **59** could then tautomerize to Nα–C5–C6-exocyclic enamine **60**. It is important to note that although the endocyclic enamine tautomer is thermodynamically preferred over the exocyclic tautomer in similar 6-membered systems, the exocyclic enamine is accessible and reactive.[12b] However, inevitable formation of the endocyclic enamine tautomer would most likely render the C4-stereocenter subject to rapid epimerization, and thus the C4-stereocenter of synthetic precursors to **60** would most likely be inconsequential to the cascade reaction.



Scheme 2.2 Proposed cascade sequence to form the pentacyclic core **46** where imine formation precedes carbon-carbon bond formation.

[21] A similar disconnection was used by Smith and Beshore in ref. 13. We anticipated that the use of the Nβ–C13–C12-enamine would greatly facilitate this transformation.

Next, stereoelectronically preferred axial attack of **60** onto the α,β-unsaturated iminium ion would afford tetracycle **61** via 7-*endo-trig* cyclization.[22] Importantly, 5-*endo-trig* cyclization from **59** should not be competitive since the resultant enamine after the initial addition is an *anti*-Bredt product. **61** is then proposed to tautomerize to afford enamine **47** as a single diastereomer; the stereochemistry generated at C7 and C12 during this process are the only stereochemical outcomes possible due to topological constraints. 6-membered enamine **47** is then poised to undergo the transannular Mannich reaction, thereby delivering the pentacyclic core **46**.

A less ambitious sequence of events, which is illustrated in Scheme 2.3, was also planned. This sequence would begin with 2-cyclohexenone **62**, which would result from either Robinson annulation of **51**/**57**[21] or direct coupling of 2-cyclohexenone anion equivalent **54** with iodide **52** (Scheme 2.1). Condensation of Nα with the C5-ketone would result in imine **63**, which could then tautomerize to the exocyclic Nα–C5–C6 enamine tautomer **64**/**65** and similarly undergo 7-*endo-trig* intramolecular cyclization to form the C6–C7 bond.[22] In this scenario, the newly formed C7-stereocenter is no longer controlled by explicit topological constraints due to the lack of the C13–Nβ bond. However, pseudo-axial attack at C7 by the enamine is again stereoelectronically required since pseudo-equatorial attack results in an intermediate that suffers severe 1,3-allylic strain. Thus only two conformations, **64** and **65**, can potentially react to form a 7-membered ring. 1,4-Conjugate addition *anti* to the C16-methyl group in **65** should be favored over *syn* 1,4-addition in **64**, which is blocked by steric hindrance.[23] This stereoelectronic argument predicts the desired stereogenicity at C7, regardless of whether a rigid topological constraint exists. After the cyclization, we anticipated that stereo-electronically favored axial protonation at C12 of the resultant enol **66** would lead to tricycle **67**.

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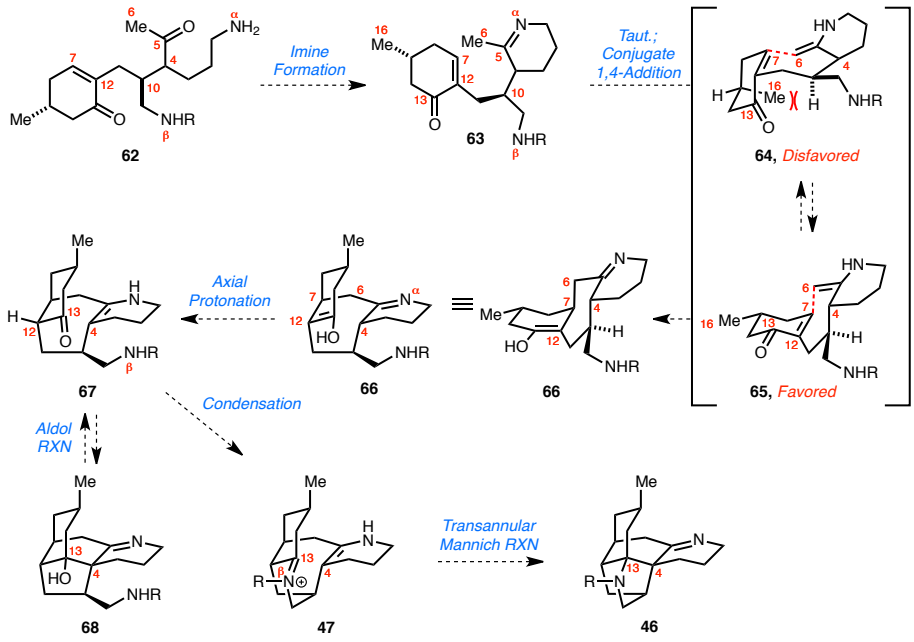
[22] As discussed in chapter one, a similar 7-*endo-trig* cyclization was employed by Smith and Beshore in ref. 13.

[23] This analysis is supported by past syntheses of *Lycopodium* alkaloids as discussed in chapter one; in particular the work of Smith and Beshore (see ref. 13) on the lyconadins clearly suggests that a 7-*endo-trig* cyclization should be stereoselective.



Scheme 2.3 An alternative proposed cascade sequence where the C16-methyl group controls the stereoselectivity of the 1,4-conjugate addition reaction.

At this juncture, it was unclear whether **67** would exist as the keto-enamine form or would react further via a transannular aldol reaction to form tetracycle **68**. We hypothesized that if the C13-ketone was kinetically accessible, then we could next initiate condensation of Nβ with the C13-ketone.[24] Notwithstanding, successful condensation would intercept intermediate **47**, which would again be poised to undergo the desired transannular Mannich reaction to form pentacyclic core **46**.

If successful, our proposed cascade reaction sequence could potentially construct up to three σ carbon-carbon bonds, two σ carbon–nitrogen bonds, and one σ carbon-hydrogen bond. We were comforted by the belief that, in practice, we could potentially break up the cascade into discrete isolable steps, and influence the order of steps by judiciously employing the appropriate nitrogen

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[24] One complication is that only the C12-epimer depicted (**67**, Scheme 2.3) can condense with Nβ due to topological constraints of the molecule. Whether the C12-stereocenter could epimerize was unknown and potentially problematic.

protecting groups. As Professor Evans stated, one “pays up front” building up and maintaining all of the reactive functionality needed to execute a cascade reaction. This wisdom certainly applied to our proposed cascade, as only two possible scenarios are described out of the multitude of reaction pathways possible with a substrate like **51**/**57**. Nonetheless, we were encouraged by past literature precedence in the arena of *Lycopodium* alkaloid synthesis, which heavily supported our proposal (albeit unbeknownst to us at the time). Interestingly, the transformation of **60** to the pentacyclic core **47** (Scheme 2.2) is in essence a formal [3+3]-cycloaddition, which is an intramolecular variant of that applied by Schumann as described in chapter one.[10] However, addition of the single C4–C10 bond added considerable challenges in not only building the correct substrate but maintaining the reactive functionality correctly poised for the ensuing cascade reaction (vide infra). In fact, the intramolecular [3+3]-cycloaddition in analogy to Schumann’s work was never successful for these reasons, as will be discussed in the upcoming sections of this chapter.

First-Generation Approach to the Core of (–)-Himeradine A and (+)-Fastigiatine

The project commenced with the synthesis of the more complex eastern fragment **52** (Scheme 2.1). This endeavor began with the construction of the requisite enantiopure building blocks, cyclopropane **55** and primary iodide **56**, which were prepared in high enantiopurity on multi-gram scale according to literature protocol.[25] With both **55** and **56** in hand, the three-component coupling of these building blocks and sodium azide was next investigated. Practically, this was done in a step-wise fashion. First, **55** underwent smooth cyclopropane opening when heated with sodium azide, triethylamine, and acetic acid (Scheme 2.4). I then found that the resultant crude primary azide underwent efficient alkylation with **56** in the presence of cesium carbonate to afford coupled product **69** in a >10:1 mixture of diastereomers. Next, saponification of both the butyrolactone and the carboethoxy group of **69** with lithium hydroxide, followed by in situ acidification with hydrochloric acid and subsequent warming, led to decarboxylation and relactonization to afford butyrolactone **70** as a 3:1 mixture of *trans:cis* C4-epimers. At this stage, all that was required to complete the desired coupling fragment **52** was the addition of the C6-carbon unit and functionalization of the latent C11-primary hydroxyl. The former objective was accomplished with addition of methyllithium to **70**, which led to hemi-ketal **71** as a complex mixture of diastereomers. All attempts to directly silylate or sulfonylate the latent primary alcohol of **71**—presumably via accessing the open chain keto-hydroxy form in situ—were unsuccessful. Formation of byproducts such as dihydrofuran **72** and ketal **73** (Scheme 2.4, box) suggested that the open chain form of **71** was not accessible and that silylation or sulfonylation of the hemi-ketal hydroxyl of **71** had occurred instead. Subsequent oxocarbenium ion formation could then result in generation of either **72** or **73**.

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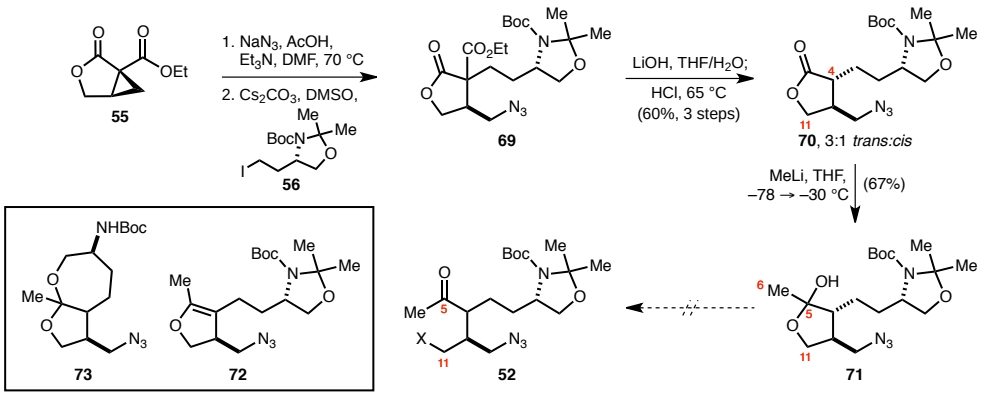
[25] See Experimental Section for more details.



Scheme 2.4 Three-component coupling of **55**, **56**, and sodium azide, as well as attempted synthesis of coupling fragment **52**.

In order to access and functionalize the C11-primary hydroxyl, formation of the Weinreb amide derivative of **70** was next pursued (Scheme 2.5). The *trans:cis* ratio of **70** was first enriched by epimerizing the C4-stereocenter with DBU to attain a >20:1 ratio of *trans:cis* C4-epimers. Although the C4-stereocenter is potentially inconsequential for the downstream cascade reaction, I sought to work with one diastereomer for the immediate forthcoming steps. Next, treatment of **70** with the aluminum amide derived from trimethylaluminum and *N*,*O*-dimethylhydroxylamine hydrochloride led to formation of the desired Weinreb amide **74**.[26] Unfortunately, **74** was extremely sensitive, as it readily cyclized back to **70** upon acidic workup or purification. Attempted sulfonylation or halogenation of the C11-primary hydroxyl of **74** was plagued with eventual problems of re-lactonization back to **70**, presumably by S_N2 displacement of a C11-activated derivative by the C5-carbonyl.[27]

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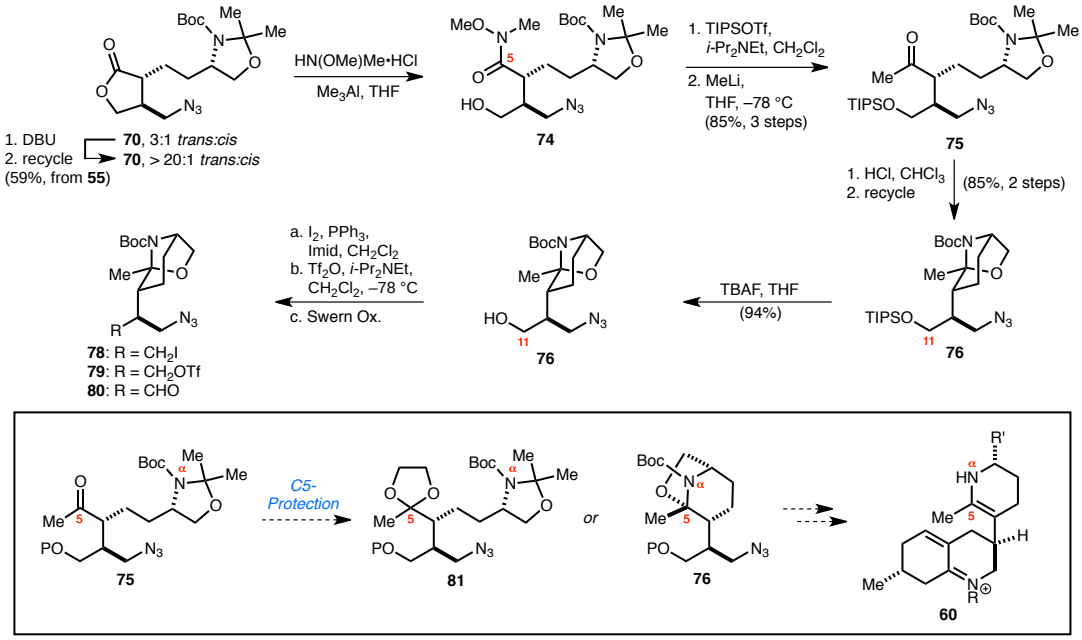
[26] Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171–4172.

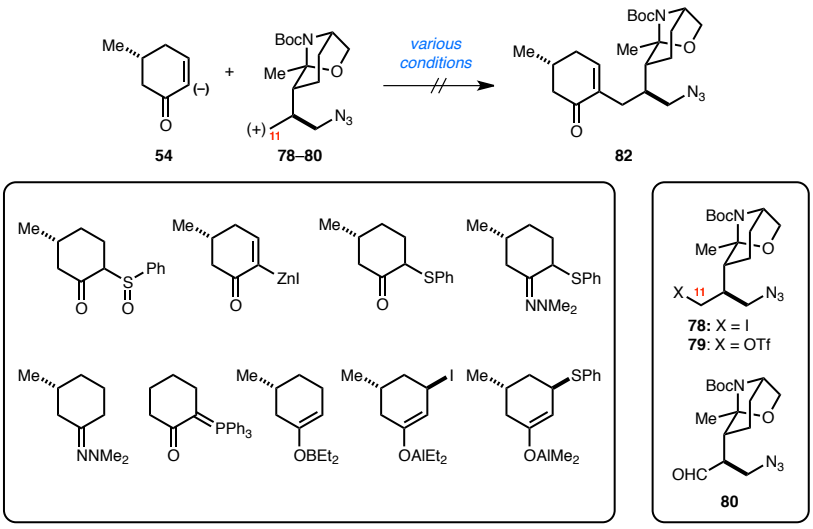
[27] Forebodingly, this unusual tendency of the C11-hydroxyl or amino derivative to engage a C5-carbonyl derivative would turn out to be a recurring problem in our synthetic efforts toward himeradine A (**38**) and fastigiatine (**37**).



Scheme 2.5 Synthesis of the eastern fragment via the formation of a bicyclic aminal.

At this juncture, it seemed logical that the C5-carbonyl had to be masked to prevent its cyclization with the proximal C11-primary hydroxyl group or its derivative. Thus silyl protection of crude **74** gave the resultant TIPS-ether and subsequent addition of methyllithium resulted in clean formation of methyl ketone **75**. Several choices of C5-carbonyl protecting groups seemed plausible, but the use of bicyclic aminal **76** (Scheme 2.5, box) was particularly interesting. Since formation of the C5–Nα bond is eventually required, formation of bicyclic aminal **76** served not only the purpose of protecting the C5-ketone but would also preemptively reduce the complexity of the upcoming cascade. After extensive experimentation, I discovered that treatment of **75** with anhydrous hydrochloric acid in chloroform led to formation of bicyclic aminal **76** in 75% yield and a mixture of mixed ketal derivatives. Re-exposure of the mixed ketal mixture to anhydrous hydrogen chloride resulted in an additional 10% of **76**. To our satisfaction, deprotection of the TIPS-ether afforded C11-primary hydroxyl **77** cleanly, which could then be either iodinated, triflated, or oxidized to the aldehyde to deliver eastern coupling fragments **78**, **79**, and **80**, respectively.

With the aforementioned eastern coupling fragments in hand, I first investigated their potential coupling with an arsenal of 2-cyclohexenone anion equivalents **54** (Scheme 2.6). The enantiopure 5-methycyclohexanone derivatives shown were generally synthesized from (*R*)-pulegone according to literature protocol,[28] and in the interest of brevity the detailed synthesis of each nucleophile will not be fully discussed. All of the nucleophiles tested were ultimately unsuccessful in accessing cascade substrate **82**. Attempted alkylation reactions with **78** and **79** were generally unsuccessful or low yielding; this poor reactivity was attributed to the steric hindrance surrounding the C11-leaving group (vide infra). More success was realized with aldol reactions with **80**. However, difficulty in cleanly eliminating the resultant hydroxyl and with the necessary subsequent alkene isomerization led us to ultimately abandon these strategies. I briefly explored the possibility of generating an organometallic species from iodide **78.** Attempted lithium halogen exchange reactions



Scheme 2.6 Attempted couplings of 2-cyclohexenone anion equivalents with the eastern fragment were ultimately unsuccessful.

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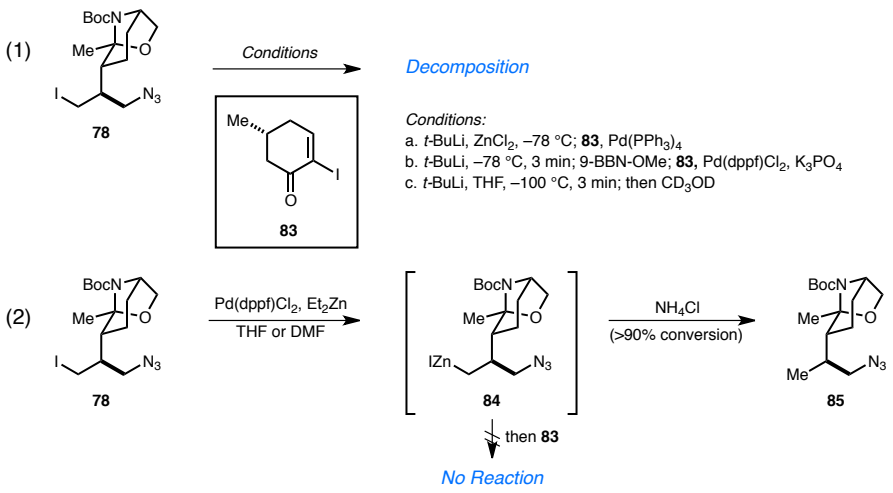
[28] (a) Kozak, J. A.; Dake, G. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 4221–4223; (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673, and references therein.



Scheme 2.7 Attempts to cross-couple an organometallic derived from iodide **78**.

followed by transmetallation and cross-coupling with 2-iodocyclohexenone **83**[29] were unsuccessful (Scheme 2.7, Eq. 1, conditions a-b), presumably due to the instability of the intermediate alkyl lithium species in the presence of the neighboring azide. I was able to successfully insert zinc via a palladium-mediated zinc insertion (Scheme 2.7, Eq. 2);[30] however, attempts to cross-couple **84** were unsuccessful.

Due to the difficulties I encountered with alkylation of iodide **78** with bulkier cyclic nucleophiles, I turned my attention to the use of smaller acyclic nucleophiles where the 2-cyclohexenone, or functional equivalent, would instead be formed by an eventual condensation between C12 and C7 as depicted earlier in Scheme 2.2 (i.e., **58** → **59**). With the acyclic dimethylhydrazone **86**, I was able to achieve alkylation with iodide **78** to afford **87** after hydrazone cleavage, albeit in low yield (Figure 2.3, Eq. 1). This result was somewhat surprising, given the successful alkylation reaction with the same hydrazone **86** employed by Smith and Beshore (Figure 2.3, Eq. 2).[13] This dichotomy could be rationalized by inspecting a simple 3D model of **78**, which

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[29] For the synthesis of **83**, see Scheme 2.10 and ref. 28b.

[30] Stadtmueller, H.; Lentz, R.; Tucker, C. E.; Stuedemann, T.; Doerner, W.; and Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027–7028.

most likely exists in a low energy conformation where approach of nucleophiles to σ*-C–I is occluded (Figure 2.3, box). In contrast, the substituents in **88** are effectively pinned back by association in a 6-membered ring, reducing the steric constraint. However, nucleophiles attacking aldehyde **80** should not suffer from the same steric occlusion since the trajectory angle is 107° and the aldehyde has two accessible faces. Furthermore, additions to **80** may benefit from closed transition states with chelation between the aldehyde and the nucleophile. These rationales are supported by our prior observations that **80** underwent aldol reactions rather efficiently. Thus logically, the use of a smaller acyclic western fragment with aldehyde **80** could potentially allow for a robust coupling reaction that did not suffer from the same downstream problems in forming the 2-cyclohexenone moeity associated with using a cyclic precursor (i.e., introducing the C12–C7 unsaturation).

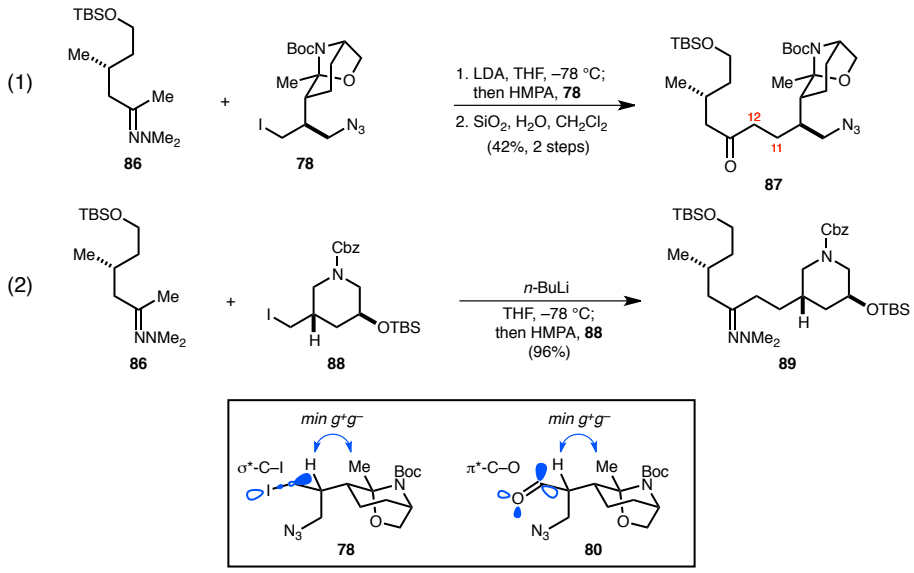
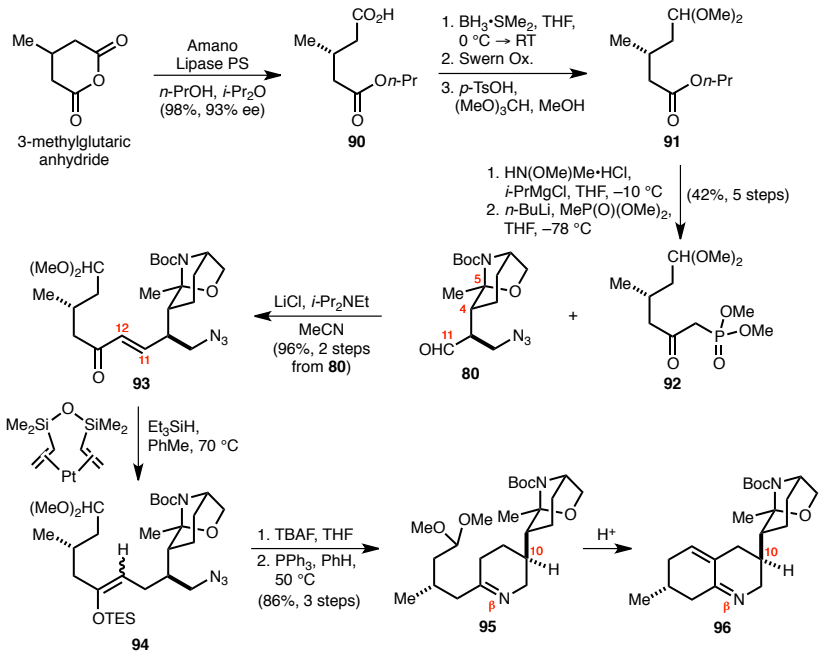


Figure 2.3 Simple rationale for the poor reactivity of iodide **78**.



Scheme 2.8 Synthesis of cascade substrate **96**.

Professor Evans instinctively proposed utilizing a Horner–Wadsworth–Emmons olefination as the key coupling reaction with aldehyde **80** and phosphonate **92** (Scheme 2.8). The synthesis of phosphonate **92** began with the lipase-mediated desymmetrization of 3-methylglutaric anhydride with *n*-propanol to provide carboxylic acid **90** in 93% ee (Scheme 2.8).[31] The carboxylic acid of **90** was transformed to dimethyl acetal **91** in a three-step process involving: (1) chemoselective reduction with borane dimethylsulfide complex, (2) oxidation of the resultant primary carbinol, and (3) dimethyl acetal formation. Subsequent conversion of **91** to the corresponding Weinreb amide[32] followed by addition of lithiated methylphosphonate afforded β-ketophosphonate **92**. To our satisfaction, Horner–

[31] Prepared according to the procedure in: Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A. *Org. Lett.* **2011**, *13*, 3758–3761.

[32] Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

Wadsworth–Emmons reaction between **92** and aldehyde **80** using Masamune-Roush conditions[33] cleanly provided base-sensitive enone **93**.[34] I next attempted to simultaneously unmask the β-amino nitrogen and reduce the superfluous C11–C12 unsaturation via hydrogenation. To our delight, imine **95** was isolated as the major product from the reaction, finally delivering a desired cascade substrate. However, substantial over-reduction to the corresponding piperidine was also observed, which could not be circumvented under a variety of conditions. A workable alternative was discovered, which involved chemoselective hydrosilylation of enone **93** with catalytic Karstedt's catalyst and triethylsilane to yield enolsilyl ether **94**.[35] Desilylation of crude **94** with TBAF, followed by treatment of the resultant ketone with triphenylphosphine on a polystyrene solid support, led to clean formation of imine **95**.

Exposure of **95** to a variety of acidic conditions led to rapid formation of crude α,β-unsaturated imine **96**[36] (Scheme 2.8), which proved to be quite unstable to air, prolonged handling, and purification. Unfortunately, attempts to drive the cascade reaction further under a variety of conditions proved fruitless. Practically, a large source of difficulty was due to the instability and highly polar nature of the products formed. Enamines are notorious for their facile aerobic oxidation and subsequent decomposition, and any cascade involving two latent basic primary amines simultaneously unmasked would prove considerably challenging. After substantial investigation, I elected to focus on a promising alternative route that was concurrently being pursued at the time.

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[33] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183–2186.

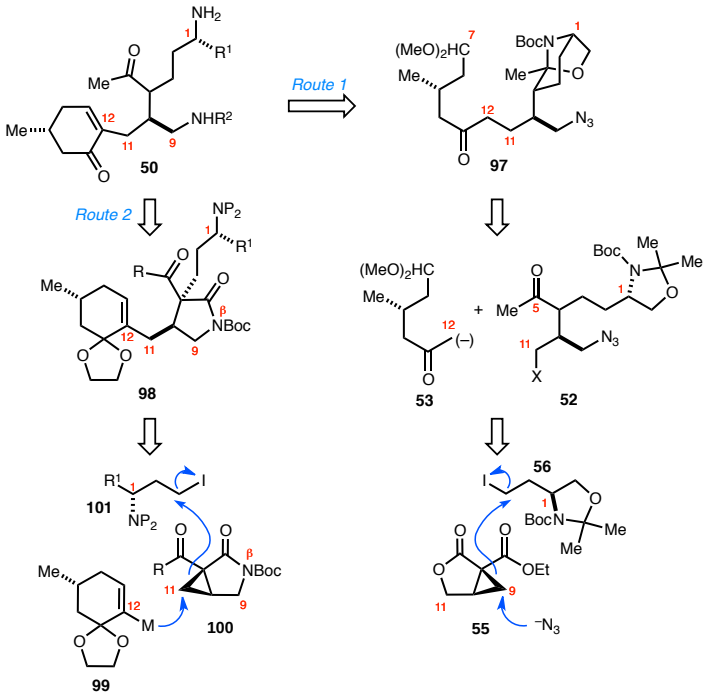
[34] The use of Hünig's base was crucial, as triethylamine readily induced β- and γ-elimination of hydrogen azide from **80** and **93**, respectively.

[35] Johnson, C. R.; Raheja, R. K. *J. Org. Chem*. **1994**, *59*, 2287–2288.

[36] Interestingly, **96** could also be accessed from **93** directly via hydrogenation under acidic conditions. See Experimental Section for more details.

Second-Generation Synthesis Plan

Due to difficulties encountered in the first-generation synthesis plan described in chapter two, a second-generation retrosynthesis of fastigiatine (**37**) and himeradine A (**38**) was designed. Both synthesis plans would still incorporate the same proposed cascade reaction sequence to generate the pentacyclic core **46** via a transannular Mannich reaction, and thus both routes would target similar cascade substrates, such as **50** (Scheme 2.9). Setbacks in reaching **50** via the original synthesis plan (Scheme 2.9, route 1) arose from two major difficulties: (1) generating a suitable precursor to form the C11–C12 bond and (2) efficient formation of the C11–C12 bond itself. A clumsy sequence had to be developed to protect the C5-carbonyl as a bicyclic aminal in order to appropriately functionalize the C11-hydroxyl, which would otherwise be bound in a closed 5-membered ring system and hence inaccessible. Additionally, the C1-hydroxymethyl group, which was installed to introduce the quinolizidine of himeradine A (**38**), was now an integral part of the bicyclic aminal and thus is critical to the success of forming the C11–C12 bond. A synthesis of fastigiatine (**37**), which lacks any



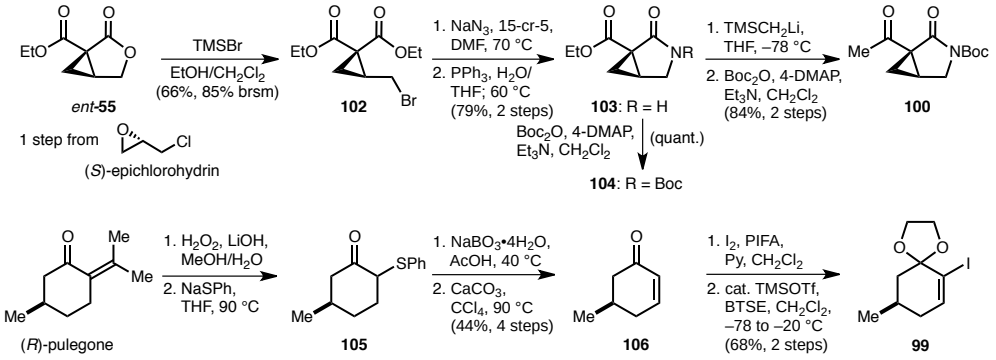
Scheme 2.9 A second-generation retrosynthesis of cascade substrate **50**.

additional carbon appendage at C1, would thus require later excision of the superfluous C1-hydroxymethyl group. Lastly, although a Horner–Wadsworth–Emmons reaction eventually proved successful in forming the C11–C12 bond of **97**, it required additional oxidation/reduction sequences at C11 and delayed installation of the C7–C12 bond.

We reasoned that if we installed the more challenging C11–C12 bond earlier in the synthesis that many of the difficulties we encountered previously could be circumvented. In particular, we hypothesized that one could exploit a hidden pseudo-C_2-symmetry evident in **50**: both C11 and C9 are functionalized methylenes where nucleophiles, a 2-cyclohexenone anion equivalent and a nitrogen moeity, have been incorporated, respectively. In the original synthesis plan, the Nβ-azide is initially introduced via nucleophilic cyclopropane opening of **55** and the C11–C12 bond is later installed. However, one could use the nucleophilic cyclopropane opening to form the C11–C12 bond earlier via the addition of organometallic **99** to cyclopropane **100**, which already contains the β-nitrogen but in a 5-membered 2-pyrrolidinone. This second-generation strategy effectively mirrors the first-generation strategy in that it uses similar transformations as its predecessor but reassigns how the C11 and C9 substituents are introduced, and simply requires the enantiomer of cyclopropane **55** as the ultimate starting material. Lastly, this new strategy would potentially be amenable to a synthesis of both fastigiatine (**37**) and himeradine A (**38**).

Synthesis of (+)-Fastigiatine

The second-generation route began with the synthesis of enantiopure cyclopropane **100** and vinyl iodide **99** (Scheme 2.10). First, a modified literature protocol was employed to construct 2-pyrrolidinone **103** and its Boc protected derivative **104**.[37] Alternatively, addition of excess (trimethylsilyl)methyllithium to **103** cleanly installed the C6-carbon unit as a methyl ketone[38] and final Boc protection afforded cyclopropane **100**. The synthesis of vinyl iodide **99** began with the preparation of 2-cyclohexenone **106** according to literature protocol,[28b] which was subsequently α-iodinated and protected as a ketal using Noyori's conditions[39] to afford **99**.



Scheme 2.10 Synthesis of cyclopropane **100** and vinyl iodide **99**.

With the requisite partners cyclopropane **100** and vinyl iodide **99** in hand, I next investigated the crucial nucleophilic cyclopropane opening to form the C11–C12 bond. I discovered that treatment of **99** with *t*-butyllithium followed by addition of the copper *t*-butyl-acetylide afforded mixed diorganocuprate **107**, which regioselectively added to C11 of cyclopropane **100** to give coupled product **108** (Scheme 2.11) in modest yield.[40] I next turned to formation of the C4–C5 bond via an

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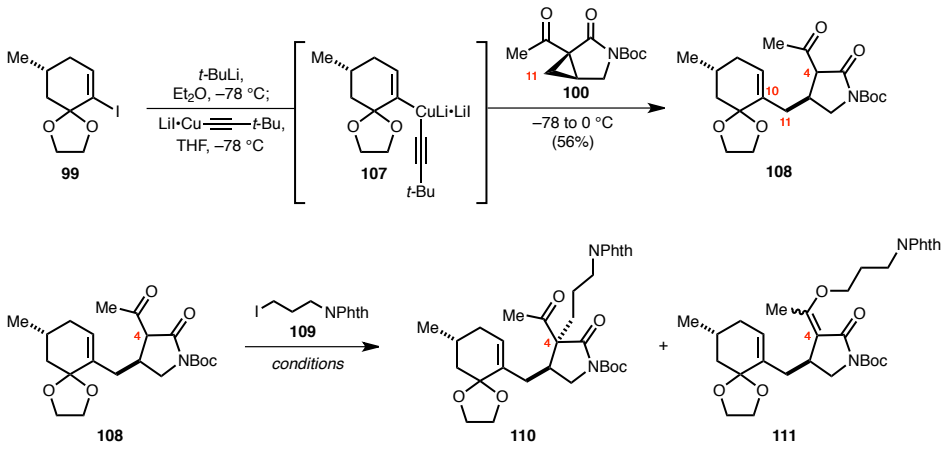
[37] Medda, A. K.; Lee, H.-S. *Synlett* **2009**, *6*, 921–924 and references therein.

[38] Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136–3138.

[39] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

[40] Majetich, G.; Leigh, A. J.; Condon, S. *Tetrahedron Lett.* **1991**, *32*, 605–608.

alkylation reaction, as was accomplished in the previous synthesis plan. However, we elected to target fastigiatine (**37**) over himeradine A (**38**) in the interest of starting with the simplest cascade reaction possible, uncomplicated by the additional C1-stereocenter. Unfortunately, I soon found that attempted alkylation of **108** with iodide **109** or its bromide analog under a variety of conditions led to at best equimolar ratios of desired alkylation product **110** and a mixture of byproducts **111** that appeared to be products of *O*-alkylation. This result was not surprising, given the steric congestion surrounding the C4-reacting center.[41]



Scheme 2.11 Coupling of iodide **99** with cyclopropane **100** and subsequent alkylation reactions.

Fortunately, I concurrently found that exposure of ethyl ester **104** to mixed organocuprate **107** led to clean nucleophilic cyclopropane opening to yield coupled product **112**. Furthermore, **112** underwent exclusive *C*-alkylation with 1-chloro-3-iodopropane to afford desired alkylated product **113** in high overall yield (Scheme 2.12). In order to obtain all of the carbon units needed for the upcoming cascade reaction, all that remained was introduction of the C6-carbon unit. I envisioned that this would be possible via the chemoselective mono-addition of an organometallic to the endocyclic C5-carbonyl of imide **113**, a reaction widely conducted with *N*-Boc protected 2-pyrrolidinones and

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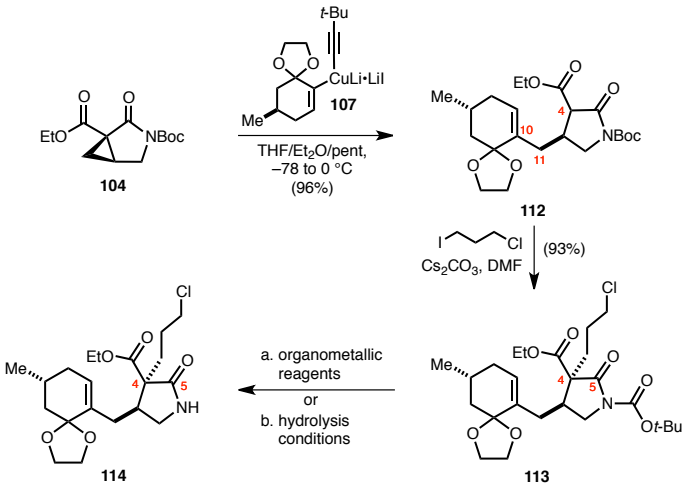
[41] Kurts, A. L.; Genkina, N. K.; Macias, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4777–4785.

valerolactams. However, several exploratory reactions with numerous organometallics, such as methylmagnesium bromide, methyllithium, and trimethylsilylmethyl lithium, led to predominant formation of Boc cleaved product **114**. In hindsight, these observations were not surprising. Chemoselective organometallic addition to the endocyclic imide carbonyl of *N*-Boc 2-pyrrolidinone is predicated on the bulky *t*-butyl group sterically protecting the exocyclic carbonyl.[42] However, in our system the endocyclic carbonyl is adjacent to the sterically congested C4-all carbon quaternary center, rendering it less available to 1,2-addition than the Boc carbonyl. I thus hypothesized that this regioselectivity could be circumvented if the C4-carboethoxy group of **113** was simply removed prior to introduction of the C6-carbon unit. Unfortunately, the C4-carboethoxy group of **113** proved recalcitrant to hydrolysis under various conditions, resulting only in Boc cleaved products. I therefore elected to replace the C4-carboethoxy group of cyclopropane **104** at an earlier stage with a carboxyester that could be easily cleaved at the appropriate time.



Scheme 2.12 Successful nucleophilic cyclopropane opening and subsequent *C*-alkylation.

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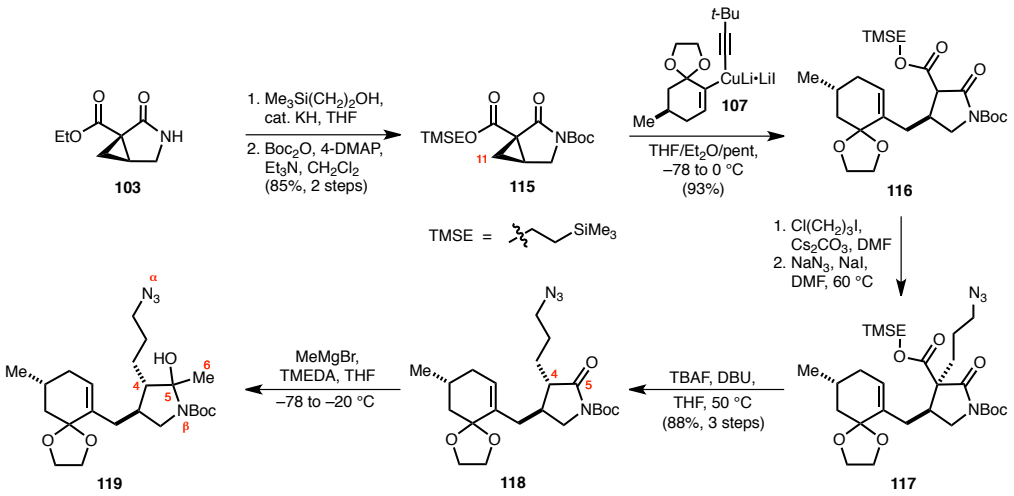
[42] Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228–234.



Scheme 2.13 Successful introduction of the C6-methyl group using a TMSE carboxyester.

Transesterification of **103** with 2-(trimethysilyl)ethanol,[43] followed by *N*-Boc formation afforded cyclopropane **115** (Scheme 2.13). Upon exposure to mixed organocuprate **107**, cyclopropane **115** similarly underwent facile opening at C11 to provide imide **116**. Conveniently, this convergent fragment coupling could be conducted on >5-gram scale. Imide **116** was then transformed to azide **117** via alkylation with 1-chloro-3-iodopropane and displacement of the resultant primary chloride with sodium azide. As hoped, exposure of **117** to TBAF induced rapid TMSE carboxyester cleavage with concomitant decarboxylation.[44] Running the decarboxylation in the presence of DBU allowed in situ base-catalyzed epimerization to yield a >10:1 mixture of C4-epimers of *N*-Boc-2-pyrrolidinone **118**.[45] Gratifyingly, addition of methylmagnesium bromide led to exclusive addition to the C5-carbonyl to give hemi-aminal **119** as a mixture of diastereomers.

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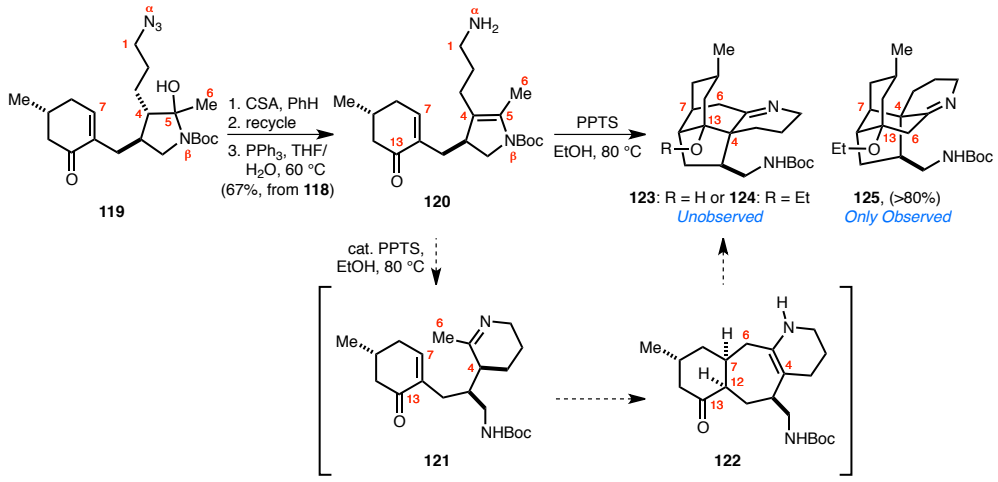
[43] Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238.

[44] Knobloch, E; Brückner, R. *Synlett* **2008**, *12*, 1865–1869.

[45] Although the C4-stereocenter of **118** is inconsequential, this epimerization facilitated characterization.



Scheme 2.14 Attempted cascade reaction with dihydropyrrole **120**.

Upon attempted purification of **119**, partial dehydration to the corresponding enamide occurred. This transformation was promoted by acid, and treatment of **119** with CSA followed by Staudinger reduction of the C1-azide yielded dihydropyrrole **120** (Scheme 2.14). I hypothesized that although the C–N bond connectivity of **120** was incorrect, **120** may still serve as a potential cascade substrate. As depicted in Scheme 2.14, I speculated that under the appropriate conditions, the more nucleophilic Nα-amine may be able to interchange with the Nβ-carbamate to give imine **121**. This was predicated on the assumption that **120** should be unable to cyclize to form the undesired C4–C7 bond since 5-*endo*-*trig* cyclization is in violation of Baldwin's rules.[46] The cascade reaction would then proceed as originally intended, potentially affording tetracycle **123** after the subsequent transannular aldol reaction of **122**. Heating **120** with pyridinium *p*-toluenesulfonic acid in ethanol led to clean formation of a new single product that had incorporated ethanol but contained roughly all of the predicted carbon and proton peaks consistent with **124**. However, upon closer inspection of HSQC and HMBC NMR data, the structure of the new product was instead consistent with the constitutional isomer **125**.

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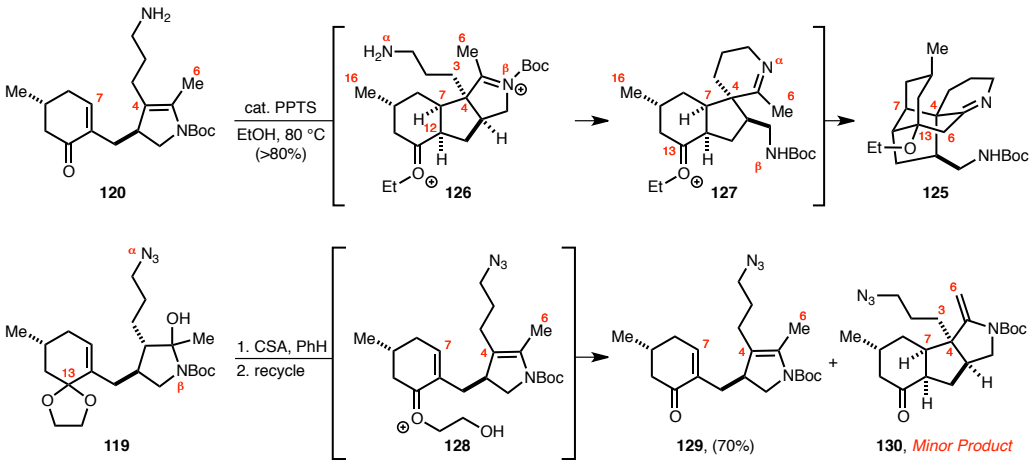
[46] (a) Baldwin, J. E. *J*. *Chem*. *Soc*., *Chem*. *Commun*., **1976**, 734–736; (b) Johnson, C. D. *Acc*. *Chem*. *Res*. **1993**, *26*, 476–482.

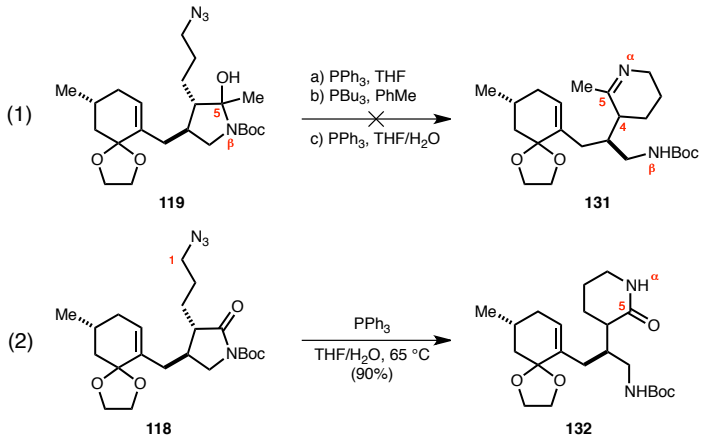


Scheme 2.15 5-*Endo-trig* cyclization is facile.

In hindsight, the formation of **125** can be easily rationalized by the mechanism outlined in Scheme 2.15. Initial formation of an oxocarbenium ion triggers a 5-*endo-trig* cyclization to form the C4–C7 bond and afford **126**; although this transformation is disfavored by Baldwin's rules, the highly charged character of the reactive species allowed an exception in this particular case. This initial bond formation is completely diastereoselective, occurring *anti* to the C16-methyl group as predicted and where the C4-stereogenecity is governed by formation of the less strained *cis*-5,5-ring fusion. The nitrogen atoms can then interchange to afford imine **127**, which can tautomerize to an exocyclic enamine and cyclize via a transannular aldol reaction to afford **125**. This disheartening result provided two important lessons: (1) the correct C–N bond connectivity was most likely required for the cascade reaction since (2) 5-*endo-trig* cyclization was facile. In fact, upon closer inspection of all of the byproducts isolated during the dehydration of **119**, exocyclic enamide **130**—the product of 5-*endo-trig* cyclization—was also isolated (Scheme 2.15).

With these lessons learned, I turned my attention toward obtaining a cascade substrate containing the desired C–N bond connectivity. Unfortunately, attempts to form the requisite C5–Nα bond and 6-membered imine from crude hemi-aminal **119** were unsuccessful (Scheme 2.16, Eq. 1). I suspected that these failures were again indicative of the strong thermodynamic preference for the 5-membered ring system containing the incorrect C5–Nβ bond, reminiscent of our experience in the

original synthesis plan with the analogous hemi-ketal. Attempts to hydrolyze the C5–Nβ bond of **118** or form the corresponding Weinreb amide were also ultimately unsuccessful, again due to problems with recyclization back to **118**. However, I eventually found that Staudinger reduction of the C1-azide led to in situ lactamization to afford valerolactam **132** (Scheme 2.16, Eq. 2), which contained the correct C–N connectivity.



Scheme 2.16 Lactamization to valerolactam **132** allows formation of the correct C–N connectivity.

A cascade one-pot sequence was developed to access valerolactam **132** from imide **116** (Scheme 2.17). Alkylation with alkyl bromide **133**, which contains a stabase-protected primary amine, followed by dilution with THF and addition of TBAF led directly to **132** in 88% overall yield. Introduction of the C6-carbon unit was next required. Attempts to form the thioamide from **132** for a subsequent Eschenmoser coupling reaction were unsuccessful; this difficulty was attributed to the proximal β-nitrogen, which may intercept any reactive intermediates or the thioamide itself in situ. In order to incorporate the C6-carbon unit, the lactam of **132** was Boc protected to give imide **135**. I planned to use the Petasis reagent[47] to incorporate the C6-carbon unit, which would also directly

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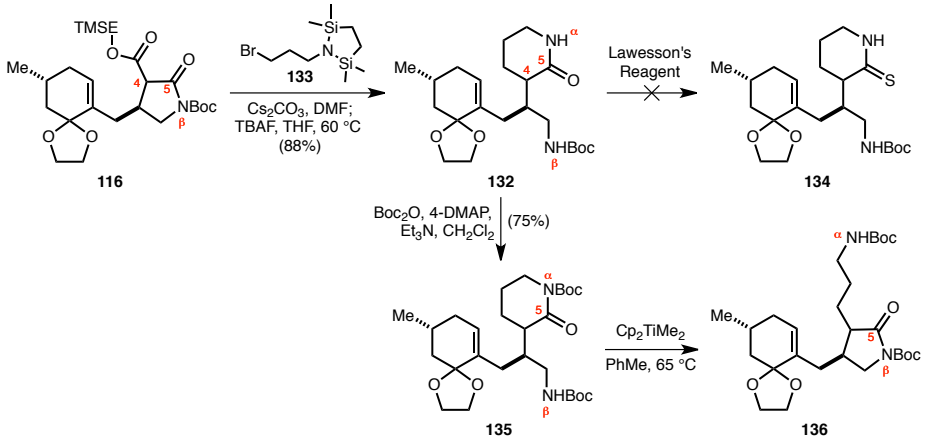
[47] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394.

deliver the necessary exocyclic enamide.[48] However, heating **135** with Petasis reagent unfortunately led to translactamization to **136**. Attempts to introduce the required C6-methylene directly with lactam **132**, such as through a Hua reaction,[49] were also unsuccessful. It became clear that another strategy was needed to generate and maintain the correct C–N connectivity.



Scheme 2.17 Attempts to incorporate the C6-carbon unit from valerolactam **132**.

I postulated that replacement of the Nβ-Boc group with a Ns group would inductively deactivate the nitrogen atom and thus reduce its propensity to form the cyclic 5-membered ring system. Mild Lewis acidic conditions employing magnesium perchlorate chemoselectively removed the Boc group of **118** in the presence of the C13-ketal (Scheme 2.18).[50] Deprotonation of the resultant amide with LiHMDS, followed by treatment with NsCl, led to clean formation of the *N*-Ns-pyrrolidinone **137**. Gratifyingly, treatment of **137** with the lithium enolate of *t*-butylacetate led to clean formation of β-ketoester **138** with Nβ completely disengaged from the C5-ketone. Exposure of

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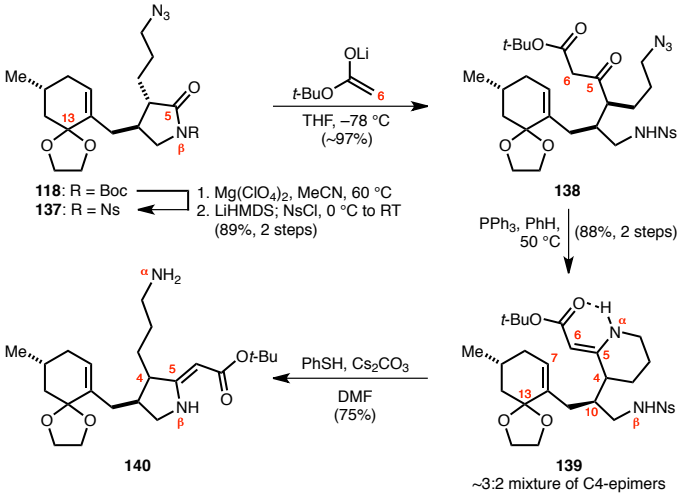
[48] For an example of methylenation of an *N*-Boc-valerolactam, see: Langlois, N. *Org*. *Lett*. **2002**, *4*, 185–187.

[49] (a) Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org*. *Lett*. **2001**, *3*, 751–754; (b) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J*. *Org*. *Chem*. **1989**, *55*, 3682–3684.

[50] Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett*. **1993**, *34*, 7873–7876.

138 to triphenylphosphine then triggered an intramolecular Staudinger reaction to construct vinylogous urethane **139** as an inconsequential ~3:2 ratio of C4-epimers.[51] It is important to note that the C6-*t*-butyloxycarbonyl served two main purposes: (1) it induced preferential formation of the exocyclic Nα–C5–C6 enamine, which would help to prevent the otherwise facile 5-*endo*-*trig* cyclization that was observed previously, and (2) it introduced greater ease of handling since vinylogous urethanes are stable, non-basic, and easily purified in comparison to their enamine counterparts.



Scheme 2.18 Inductive deactivation of Nβ allows for formation of the correct C–N connectivity.

I next sought to deprotect the Nβ-Ns group and C13-ketal, and subsequently form the C13–Nβ bond and resultant iminium ion to initiate the cascade sequence. However, deprotection of the Nβ-Ns of **139** under standard conditions[52] afforded 5-membered vinylogous urethane **140** after a facile transamination reaction (Scheme 2.18). Clearly, the Nβ-Ns group was crucial to maintaining the correct C–N bond connectivity, and would have to be removed at a later stage. Consequently, I attempted direct 1,4-conjugate addition to the latent 2-cyclohexenone of **139**. Remarkably, exposure

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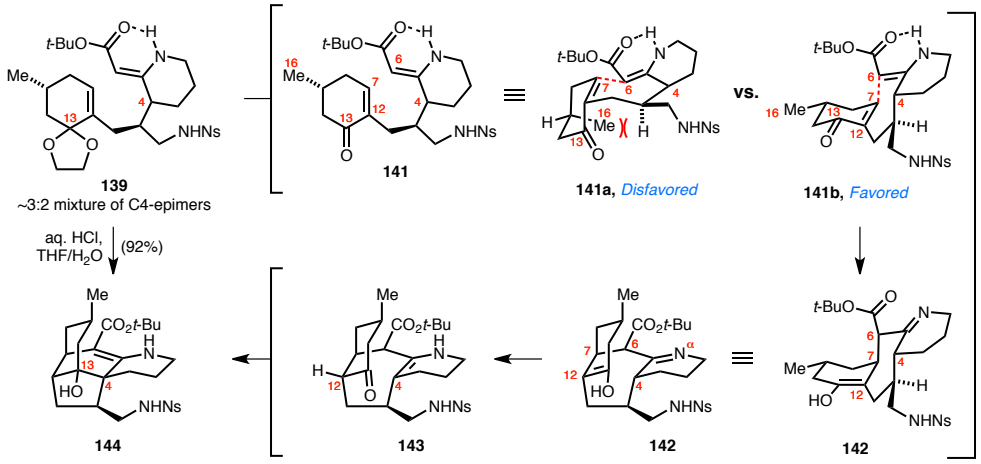
[51] Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352–5356.

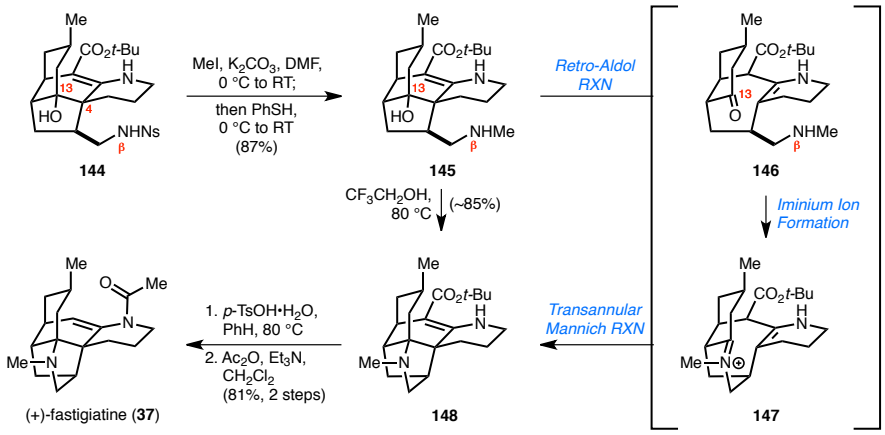
[52] Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

of **139** to aqueous hydrochloric acid led to tetracycle **144** as a single diastereomer in 92% yield (Scheme 2.19). As discussed previously, this formal [3+3]-cycloaddition[12] is believed to occur via initial C13-dioxolane cleavage, 7-*endo-trig* intramolecular 1,4-conjugate addition to form the C6–C7 bond, stereoelectronically favored axial protonation to secure the C12 stereocenter, and finally a transannular aldol reaction to form the C4–C13 bond. Again, the high diastereoselectivity of the initial 7-*endo-trig* cyclization can be rationalized by stereoelectronically favored axial attack *anti* to the C16-methyl group.



Scheme 2.19 A formal [3+3]-reaction efficiently constructs tetracycle **144**.

Completion of the pentacyclic core of fastigiatine (**37**) required exchanging the C13-tertiary hydroxyl with Nβ, presumably via an initial retro-aldol reaction, subsequent iminium ion formation, and final transannular Mannich reaction. To this end, alkylation of **144** with iodomethane in the presence of potassium carbonate, followed by subsequent addition of thiophenol, yielded tetracyclic *N*-methylamine **145** (Scheme 2.20).[52] Up until this point, there was no evidence that **145** or prior tetracyclic intermediates were in equilibrium with the retro-aldol product **146**. However, submission of **145** to electrospray ionization mass spectrometry revealed a large ion with mass corresponding to the molecular formula M–H_2O, which is the mass of the desired pentacycle **148**.



Scheme 2.20 Completion of (+)-fastigiatine (**37**).

This result hinted that the desired transformation had occurred during the ionization conditions in the mass spectrometer. Inspired, I attempted heating **145** in various common solvents. Unfortunately, heating under neutral conditions led to no reaction while the use of acids led to clean decarboxylation to the corresponding imine. I postulated that while an acid catalyst may facilitate the retro-aldol reaction, it would also protonate Nβ, thus disfavoring formation of the charged intermediates involved in the requisite retro-aldol reaction. Therefore, the use of a strong hydrogen-bond donor that was not a strong acid may logically facilitate the desired reaction. Gratifyingly, heating **145** in rigorously deoxygenated 2,2,2-trifluoroethanol cleanly afforded pentacycle **148** in 85% yield. Treatment of **148** with *p*-toluenesulfonic acid induced facile *t*-butyloxycarbonyl loss to yield the corresponding imine, which upon treatment with acetic anhydride and triethylamine afforded (+)-fastigiatine (**37**) ($[\alpha]^{24}_{D}$ = +375 (*c* = 1.4, $CHCl_3$)).[53] The ^{1}H and ^{13}C NMR spectra for synthetic (+)-**37** matched those reported for the natural compound, and the structure of synthetic (+)-**37** was unequivocally established via single crystal X-ray diffraction analysis (Figure 2.4).

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[53] The reported optical rotation for (+)-fastigiatine (**37**), which contains a minor amount of des-*N*-methylfastigiatine, is ($[\alpha]^{23}_{D}$ = +290 (*c* = 1.36, $CHCl_3$). See ref 15a.

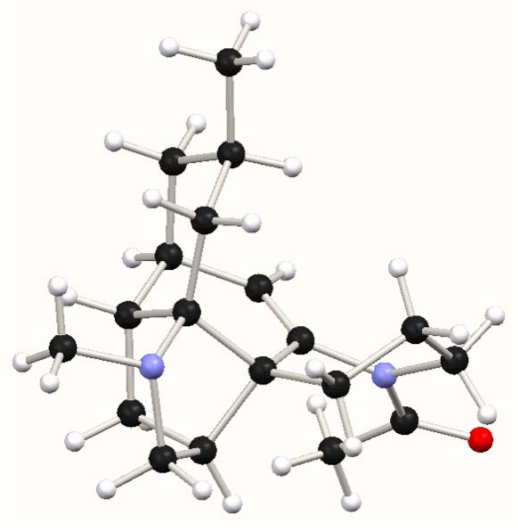

Figure 2.4 X-Ray crystal structure of (+)-fastigiatine (**37**).

Conclusion

In conclusion, the first total synthesis of (+)-fastigiatine (**37**) was completed. As described in chapter two, a first-generation synthesis plan utilizing a unique bicyclic aminal allowed us to obtain the desired cascade substrate containing the correct C–N connectivity. However, the cascade substrate ultimately proved impractical due to the difficulties associated with handling basic nitrogen compounds and air-sensitive imine/enamine tautomers. The second-generation synthesis plan described within this chapter benefited from the lessons learned from the original plan, and a similar but more streamlined design allowed for the more efficient synthesis of the cascade substrate. This redesign led to a convergent fragment coupling utilizing a nucleophilic cyclopropane coupling, which is one of the most complex reported to date.

Yet problems with attaining the correct C–N connectivity—neatly solved in the first-generation route with the bicyclic aminal—almost derailed the second-generation synthetic effort. The simple use of a strongly electron-withdrawing Ns group ultimately allowed for the successful formal [3+3]-cycloaddition reaction, which generated four contiguous stereocenters of fastigiatine (**37**). An unsual retro-aldol, iminium ion formation, and transannular Mannich reaction sequence was then achieved for the construction of the strained pentacyclic core of **37**. The ease of the transannular Mannich reaction sequence suggests that iminium ion **47** is at the very least a feasible biosynthetic intermediate. Overall, the second-generation synthesis plan accomplished a total synthesis of **37** in fifteen steps from known cyclopropane **104** in ~30% overall yield.

With the knowledge gained from both the first-generation and second-generation route, I am confident that a synthetic route employing the originally proposed cascade sequence with both amines working in concert could eventually be accomplished to complete a synthesis of both fastigiatine (**37**) and himeradine A (**38**). However, I decided that the pursuit of other target molecules may prove more interesting, and those efforts are described in the upcoming chapter.

Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried glassware under a positive pressure of argon unless otherwise noted. Where necessary (so noted), reactions were performed in Schlenk tubes fitted with a PTFE stopcock or pressure tubes fitted with a PTFE bushing. Flash column chromatography was performed as described by Still et al. employing silica gel 60 (40-63 μm, Whatman).[54] Where necessary (so noted), silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing triethylamine (Et_3N) or 30% (w/v) ammonium hydroxide (NH_4OH). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F_{254} plates. TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to an acidic solution of *p*-anisaldehyde (anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$), or a solution of ninhydrin in *n*-butanol followed by heating on a hot plate.

Materials. Commercial reagents and solvents were used as received with the following exceptions: tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), HMDS, benzene (PhH), toluene (PhMe), and *N*,*N*-dimethylformamide (DMF) were degassed with argon and passed through a solvent purification system (designed by J.C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al.[55] Et_3N and diisopropylamine were distilled over calcium hydride immediately before use. TMSOTf was distilled before use. Potassium hydride was washed with pentane and dried under reduced pressure before use. The molarities of *n*-butyllithium, *t*-butyllithium, methyllithium, and trimethylsilylmethyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of at least three

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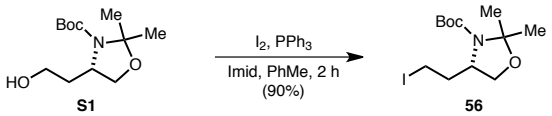
[54] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[55] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

determinations). Where necessary (so noted), solutions were degassed by alternating freeze (liquid nitrogen)/evacuation/thaw cycles (FPT, three iterations).

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 600 or Varian INOVA 500 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.16, CD_2HCN: δ 1.94). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian INOVA 500 or Varian Mercury 400 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.4, CD_3CN; δ 118.7). Infrared (FTIR) spectra were recorded on a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. FTIR Data is reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy (MS) experiments on an Agilent 6210 TOF LC/MS. Optical rotations were measured on a Jasco P-2000 digital polarimeter with a sodium lamp. Reported readings are the average of at least three measurements for each sample. The structure of (+)-fastigiatine (**37**) was obtained with the assistance of Dr. Shao-Liang Zheng at the X-ray diffraction facility of the Department of Chemistry and Chemical Biology, Harvard University.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with **S1**).*



Iodide 56: Iodine (28.7 g, 113 mmol, 1.36 equiv) was added in a single portion to a stirred solution of triphenylphosphine (26.1 g, 100 mmol, 1.20 equiv) and imidazole (8.48 g, 125 mmol, 1.50 equiv) in toluene (150 mL). The solution was stirred for 5 min before a solution of **S1**[56] (20.4 g, 83.0 mmol, 1.00 equiv) in toluene (100 mL) was added dropwise via cannula. The transfer was completed with two additional portions of toluene (2 × 25 mL). The resultant heterogeneous red solution was stirred vigorously in the dark. After 2 h, saturated aqueous Na_2SO_3 solution (200 mL) was added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 20% EtOAc in hexanes) to afford known iodide **56**[57] (27.5 g, 90%) as a red solid.

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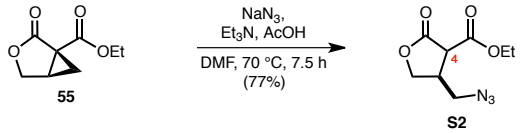
[56] Prepared in four steps from L-lysine on multi-gram scale following a literature protocol: Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Klemann, P. *Org. Lett.* **2005**, *7*, 1423–1426.

[57] For full characterization data, see: Suhartono, M.; Schneider, A. E.; Dürner, G.; Göbel, M. W. *Synthesis* **2010**, *2*, 293–303.



Azide S2:[58] Sodium azide (6.16 g, 94.7 mmol, 1.30 equiv) was added in a single portion to a stirred solution of cyclopropane **55**[59] (12.4 g, 72.9 mmol, 1.00 equiv) in DMF (80 mL). Et_3N (2.03 mL, 14.6 mmol, 0.20 equiv) and glacial acetic acid (5.42 mL, 94.7 mmol, 1.30 equiv) were then added sequentially dropwise via syringe to the stirred reaction mixture. The resultant vigorously stirred reaction mixture was then heated to 70 °C. After 7.5 h, the reaction mixture was cooled to ambient temperature, and then cautiously poured into a stirred solution of 1:1 Et_2O/saturated aqueous $NaHCO_3$ solution (~200 mL) at 0 °C. After gas evolution had ceased, the layers were separated and the aqueous layer was extracted with Et_2O (4 × 200 mL). The combined organic layers were then washed with water (5 × 400 mL) and brine (400 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford analytically pure azide **S2**[60] (12.0 g, 77%) as a light tan oil that was carried forward without further purification.

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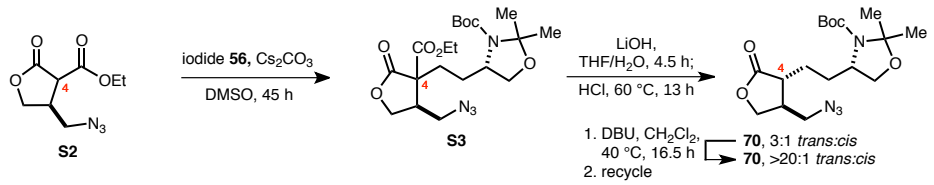
[58] This procedure was adapted from: Ok, T.; Jeon, A.; Lee, J.; Lim, J. H.; Hong, C. S.; Lee, H.-S. *J. Org. Chem.* **2007**, 7390–7393.

[59] Prepared in one step from diethylmalonate and (*R*)-epichlorohydrin according to ref. 58.

[60] For full characterization data, see ref. 58.



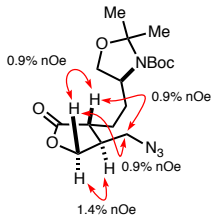
Butyrolactone 70: Cesium carbonate (37.2 g, 113 mmol, 2.00 equiv) was added in a single portion to a stirred solution of azide **S2** (12.0 g, 56.5 mmol, 1.00 equiv) in DMSO (140 mL). After 1 h, a solution of iodide **56** (27.5 g, 77.4 mmol, 1.37 equiv) in DMSO (30 mL) was added dropwise via cannula to the stirred reaction mixture. The transfer was completed with two additional portions of DMSO (2 × 10 mL). After 45 h, the reaction mixture was partitioned with saturated aqueous NH_4Cl solution (200 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (4 × 250 mL), and the combined organic layers were washed with water (5 × 400 mL) and brine (400 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude alkylated product **S3** as a >10:1 mixture of C4-epimers that was used without further purification.

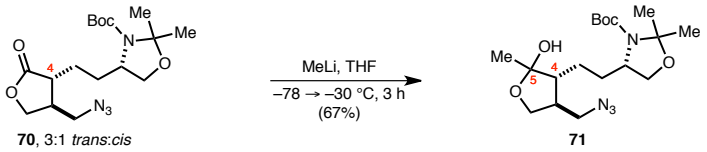
An aqueous solution of LiOH (1 M, 125 mL, 124 mmol, 2.20 equiv) was added to a stirred solution of crude **S3** in THF (550 mL). After 4.5 h, the reaction mixture was acidified with aqueous HCl (1 M) until the pH was adjusted to between pH 4 and pH 5. The resultant vigorously stirred biphasic solution was heated to 60 °C. After 13 h, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude butyrolactone **70** as a ~3:1 mixture of *trans:cis* C4-epimers, which was used without further purification.

DBU (1.69 mL, 11.3 mmol, 0.20 equiv) was added dropwise via syringe to a stirred solution of crude **70** in CH_2Cl_2 (550 mL), and the resultant reaction mixture was then refluxed at 40 °C. After 16.5 h, the reaction mixture was cooled to ambient temperature before the solution was concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel, eluent: gradient, 20% → 33% EtOAc in hexanes) to afford butyrolactone **70** (13.5 g) as a

>20:1 mixture of *trans:cis* C4-epimers. The mixed fractions containing lower *trans:cis* ratios were combined, concentrated, and re-subjected to the aforementioned experimental procedure. Flash column chromatography (silica gel, eluent: gradient, 20% → 33% EtOAc in hexanes) afforded additional material (2.4 g), which when combined with the previous batch provided butyrolactone **70** (15.9 g, 76%) as an off-white solid. **^{1}H NMR** (600 MHz, CD_3CN, 65 °C) δ: 4.35 (t, *J* = 8.6 Hz, 1H), 3.96–3.92 (m, 2H), 3.82 (br. s., 1H), 3.73 (dd, *J* = 1.5, 8.8 Hz, 1H), 3.58 (dd, *J* = 5.6, 12.6 Hz, 1H), 3.50 (dd, *J* = 7.0, 12.9 Hz, 1H), 2.59–2.51 (m, 1H), 2.42 (td, *J* = 5.9, 8.6 Hz, 1H), 1.80–1.67 (m, 3H), 1.66–1.58 (m, 1H), 1.54 (s, 3H), 1.47 (s, 9H), 1.45 (s, 3H), 1.11–1.07 (m, 1H). **^{13}C NMR** (126 MHz, CD_3CN, 65 °C) δ: 179.8, 153.8, 95.1, 81.1, 70.4, 68.6, 58.9, 54.2, 44.0, 42.0, 32.2, 29.5, 28.2, 27.3, 25.0. **FTIR** (thin film) cm^{-1}: 2978, 1774, 1689, 1389, 1365, 1256, 1169, 1094, 1022. **HRMS** (ESI) (*m/z*) calc'd for $C_{17}H_{29}N_4O_5$ $[M+H]^+$: 369.2133, found 369.2135. **TLC** (33% EtOAc in hexanes), R_f: 0.34 ($KMnO_4$).

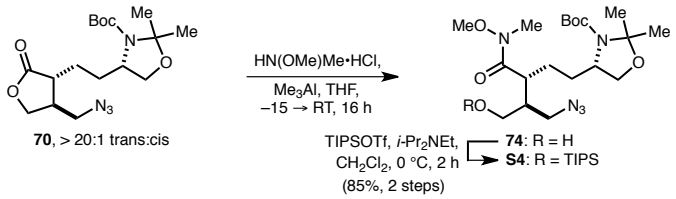
NOESY1D (500 MHz, CD_3CN):





70, 3:1 *trans*:*cis* **71**

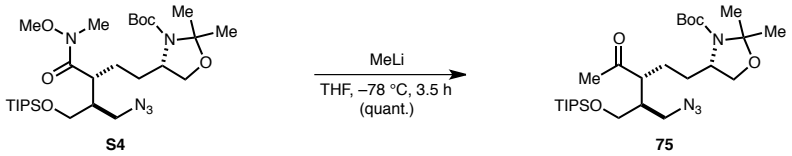
Hemi-ketal 71: A solution of methyllithium in Et_2O (1.51 M, 265 µL, 0.400 mmol, 1.20 equiv) was added dropwise via syringe to a stirred solution of butyrolactone **70** (123 mg, 0.330 mmol, 1.00 equiv) in THF (3.3 mL) at –78 °C. The resultant stirred reaction mixture was slowly allowed to warm to –30 °C over 3 h, at which point saturated aqueous NH_4Cl solution (5 mL) and Et_2O (5 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10% → 35% EtOAc in CH_2Cl_2) to afford recovered **70** (15 mg, 12%) and hemi-ketal **71** (85 mg, 67%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$, complex mixture of diastereomers; major diastereomer reported) δ: 3.98–3.88 (m, 2H), 3.84–3.70 (m, 2H), 3.53–3.47 (m, 2H), 3.44 (br. s., 1H), 3.29 (dd, *J* = 8.2, 12.3 Hz, 1H), 2.26–2.19 (m, 1H), 2.17 (s, 3H), 1.77–1.64 (m, 1H), 1.63–1.48 (m, 5H), 1.46–1.41 (m, 12H), 1.37 (s, 3H). **^{13}C NMR** (126 MHz, CD_3CN, 65 °C) δ: 153.2, 108.1, 106.5, 105.9, 94.6, 80.8, 80.3, 69.4, 68.2, 67.7, 62.0, 61.0, 59.1, 58.5, 55.7, 55.4, 52.5, 52.3, 52.2, 51.3, 51.1, 45.8, 43.4, 34.0, 33.1, 32.7, 32.1, 31.2, 29.1, 28.4, 27.5, 27.3, 27.1, 26.7, 25.4, 24.3, 23.9. **FTIR** (thin film) cm^{-1}: 3441, 2978, 2933, 1691, 1390, 1377, 1256, 1172, 1093. **HRMS** (ESI) (*m/z*) calc'd for $C_{18}H_{32}N_4NaO_5$ $[M+Na]^+$: 407.2265, found 407.2268. **TLC** (33% EtOAc in hexanes), R_f: 0.29 (anis).



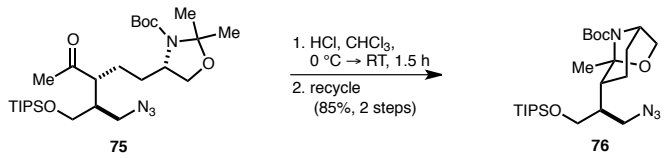
Weinreb amide S4: A solution of trimethylaluminum in hexanes (2.0 M, 49 mL, 98 mmol, 3.1 equiv) was added dropwise via syringe to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (9.71 g, 97.6 mmol, 3.07 equiv) in THF (120 mL) at 0 °C. The resultant stirred solution was allowed to warm to ambient temperature, and after 30 min was cooled back to –15 °C before a solution of butyrolactone **70** (11.7 g, 31.8 mmol, 1.00 equiv) in THF (25 mL) was added dropwise via cannula. The resultant stirred reaction mixture was slowly allowed to warm to ambient temperature over the course of 3.5 h. After an additional 12.5 h, the reaction mixture was cooled to 0 °C and then subsequently added dropwise via cannula to a stirred solution of 2:1 saturated aqueous potassium sodium tartrate solution and saturated aqueous $NaHCO_3$ solution (750 mL) at –5 °C. The stirred solution was then diluted with Et_2O (250 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 250 mL), and the combined organic layers were then washed with water (500 mL) and brine (2 × 500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude Weinreb amide **74**, which was used without further purification.

Triisopropylsilyl trifluoromethanesulfonate (9.70 mL, 36.1 mmol, 1.14 equiv) was added dropwise via syringe to a stirred solution of crude **74** and diisopropylethylamine (7.20 mL, 41.3 mmol, 1.30 equiv) in CH_2Cl_2 (160 mL) at 0 °C. After 2 h, saturated aqueous $NaHCO_3$ solution (200 mL) and CH_2Cl_2 (200 mL) were added to the stirred solution, which was subsequently allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were then washed with aqueous HCl (1 M, 3 × 250 mL) and a saturated aqueous $NaHCO_3$ solution (250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 11% → 17% EtOAc in hexanes) to afford TIPS-

protected Weinreb amide **S4** (15.9 g, 85%) as a colorless oil. **^{1}H NMR** (500 MHz, C_6D_6, 70 °C) δ: 3.88–3.74 (m, 3H), 3.72 (dd, *J* = 5.7, 8.7 Hz, 1H), 3.69–3.62 (m, 2H), 3.33 (dd, *J* = 5.6, 12.2 Hz, 1H), 3.27 (s, 3H), 3.18–3.11 (m, 1H), 2.91 (s, 3H), 2.24–2.16 (m, 1H), 1.92–1.53 (m, 7H), 1.51 (br. s., 3H), 1.46 (s, 9H), 1.41–1.28 (m, 2H), 1.18–1.06 (m, 21H). **^{13}C NMR** (126 MHz, C_6D_6, 70 °C) δ: 176.2, 152.6, 94.3, 79.7, 67.8, 63.1, 61.4, 58.3, 50.8, 44.6, 40.3, 32.8, 32.6, 29.0, 27.9, 26.3, 24.6, 18.6, 12.9. **FTIR** (thin film) cm^{-1}: 2940, 2866, 1695, 1661, 1462, 1387, 1365, 1257, 1175, 1097. **HRMS** (ESI) (*m/z*) calc'd for $C_{28}H_{56}N_5O_6Si$ $[M+H]^+$: 586.3994, found 586.4002. **TLC** (33% EtOAc in hexanes), R_f: 0.59 ($KMnO_4$).

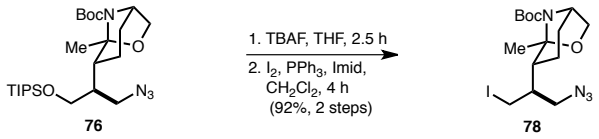


Methyl ketone 75: A solution of methyllithium in Et_2O (1.75 M, 5.14 mL, 9.00 mmol, 3.00 equiv) was added dropwise via syringe to a stirred solution of Weinreb amide **S4** (1.76 g, 3.00 mmol, 1.00 equiv) in THF (30 mL) at –78 °C. After 3.5 h, a saturated aqueous NH_4Cl solution (12 mL) was added rapidly via syringe to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The reaction mixture was diluted with Et_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford analytically pure methyl ketone **75** (1.62 g, quant.) as a pale yellow oil. **^{1}H NMR** (600 MHz, CD_3CN, 65 °C) δ: 3.92 (dd, *J* = 5.9, 8.8 Hz, 1H), 3.79 (br. s., 1H), 3.72–3.66 (m, 3H), 3.52 (dd, *J* = 5.0, 12.6 Hz, 1H), 3.38 (dd, *J* = 6.4, 12.3 Hz, 1H), 2.79–2.72 (m, 1H), 2.15 (s, 3H), 2.10–2.06 (m, 1H), 1.64–1.56 (m, 1H), 1.51 (s, 3H), 1.46 (s, 9H), 1.55–1.44 (m, 3H), 1.44 (s, 3H), 1.16–1.07 (m, 21H). **^{13}C NMR** (100 MHz, CD_3CN, 65 °C) δ: 212.0, 153.8, 95.1, 81.1, 68.6, 64.2, 59.0, 52.7, 51.8, 44.4, 33.1, 31.3, 29.6, 28.3, 25.6, 25.1, 19.3, 13.8. **FTIR** (thin film) cm^{-1}: 2941, 2866, 1694, 1462, 1364, 1256, 1173, 1093, 882, 682. **HRMS** (ESI) (*m/z*) calc'd for $C_{27}H_{53}N_4O_5Si$ $[M+H]^+$: 541.3780, found 541.3785. **TLC** (25% EtOAc in hexanes), R_f: 0.58 (anis).



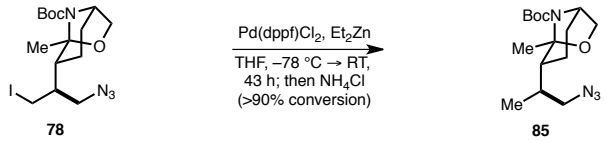
75 **76**

Bicyclic aminal 76: A solution of anhydrous HCl in dioxane (4.0 M, 3.6 mL, 14 mmol, 1.3 equiv) was added dropwise via syringe to a stirred solution of methyl ketone **75** (5.91 g, 10.9 mmol, 1.00 equiv) in $CHCl_3$ (350 mL) at 0 °C, which was subsequently allowed to warm to ambient temperature. After 1.5 h, a saturated aqueous $NaHCO_3$ solution (250 mL) was added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10% → 100% EtOAc in hexanes) to afford bicyclic aminal **76** (4.15 g, 79%) as a colorless gel and a mixture of byproducts (~1 g). The mixture of byproducts was re-subjected to the aforementioned experimental procedure to yield additional **76** (0.32 g, 6%), which was combined with the previous material. **^{1}H NMR** (500 MHz, CD_3CN) δ: 4.27–4.21 (m, 1H), 3.87–3.76 (m, 4H), 3.61 (dd, *J* = 9.0, 10.0 Hz, 1H), 3.15 (dd, *J* = 9.7, 12.7 Hz, 1H), 2.39–2.30 (m, 1H), 2.10–2.00 (m, 1H), 1.78–1.69 (m, 1H), 1.68–1.61 (m, 1H), 1.58 (s, 3H), 1.60–1.54 (m, 1H), 1.43 (s, 9H), 1.15–1.02 (m, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 153.3, 96.3, 80.9, 69.9, 64.0, 57.2, 50.7, 43.7, 42.6, 29.2, 29.0, 24.4, 19.5, 18.9, 13.2. **FTIR** (thin film) cm^{-1}: 2942, 2866, 1698, 1365, 1161, 1091, 882, 681. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{47}N_4O_4Si$ $[M+H]^+$: 483.3361, found 483.3367. **TLC** (11% EtOAc in hexanes), R_f: 0.26 (anis).

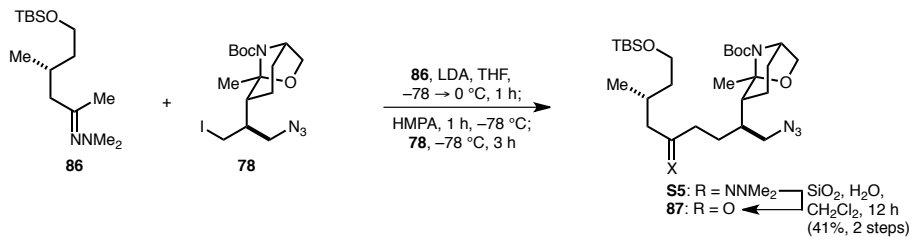


Iodide 78: A solution of TBAF in THF (1.0 M, 0.96 mL, 0.96 mmol, 1.2 equiv) was added to a stirred solution of bicyclic aminal **76** (385 mg, 0.800 mmol, 1.00 equiv) in THF (4 mL). After 2.5 h, brine (10 mL) and EtOAc (10 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the corresponding crude primary alcohol, which was used without further purification.

Iodine (406 mg, 1.60 mmol, 2.00 equiv) was added in a single portion to a stirred solution of triphenylphosphine (409 mg, 1.56 mmol, 1.95 equiv) and imidazole (272 mg, 4.00 mmol, 5.00 equiv) in CH_2Cl_2 (5 mL). The solution was stirred for 5 min before a solution of crude primary alcohol in CH_2Cl_2 (2 mL) was added dropwise via cannula. The transfer was completed with two additional portions of CH_2Cl_2 (2 × 500 μL). After 4 h, water (20 mL) and CH_2Cl_2 (20 mL) were added to the stirred reaction mixture, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% EtOAc in pentane) to afford iodide **78** (320 mg, 92%) as a colorless oil. **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.06 (br. s., 1H), 3.59 (dd, *J* = 3.8, 12.7 Hz, 1H), 3.56 (ddd, *J* = 1.5, 5.2, 7.0 Hz, 1H), 3.23 (d, *J* = 7.3 Hz, 1H), 3.15 (dd, *J* = 5.2, 10.0 Hz, 1H), 2.77 (br. s., 1H), 2.50 (t, *J* = 9.8 Hz, 1H), 2.32 (ddd, *J* = 3.3, 5.1, 11.5 Hz, 1H), 1.92 (dq, *J* = 3.5, 8.9 Hz, 1H), 1.79–1.67 (m, 1H), 1.58 (s, 3H), 1.45 (s, 9H), 1.09–0.99 (m, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 152.6, 95.0, 80.4, 69.1, 56.3, 52.1, 45.9, 41.8, 28.8, 28.1, 24.0, 18.2, 8.0. **FTIR** (thin film) cm^{-1}: 2940, 1695, 1366, 1312, 1172, 1091, 864. **HRMS** (ESI) (*m/z*) calc'd for $C_{15}H_{26}IN_4O_3$ $[M+H]^+$: 437.1044, found 437.1046. **TLC** (25% EtOAc in hexanes), R_f: 0.54 (anis).



Zinc–Iodine Exchange: Diethylzinc (11.0 µL, 0.100 mmol, 2.00 equiv) was added dropwise via syringe to a stirred solution of iodide **78** (21.8 mg, 0.0500 mmol, 1.00 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (4.0 mg, 0.005 mmol, 0.10 equiv) in THF (150 µL) at –78 °C, which was subsequently allowed to warm to ambient temperature after 5 min. After 24 h, the stirred reaction mixture was cooled to –78 °C before additional diethylzinc (11.0 µL, 0.100 mmol, 2.00 equiv) was added dropwise via syringe. The resultant stirred reaction mixture was then allowed to warm to ambient temperature. After an additional 19 h, saturated aqueous NH_4Cl solution (5 mL) and Et_2O (5 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude residue showed >90% conversion of iodide **78** to reduced product **85**. An analytical sample of **85** was obtained by flash column chromatography (silica gel, 13% EtOAc in hexanes). **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.04 (br. s., 1H), 3.65–3.56 (m, 2H), 3.26 (d, *J* = 7.3 Hz, 1H), 2.76 (t, *J* = 10.1 Hz, 1H), 1.97–1.81 (m, 2H), 1.74 (s, 3H), 1.71–1.60 (m, 1H), 1.41 (s, 9H), 1.26–1.16 (m, 2H), 1.09 (dd, *J* = 2.7, 13.0 Hz, 1H), 0.77 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 152.5, 95.5, 79.9, 69.1, 56.3, 54.6, 48.1, 34.2, 28.8(2), 24.0, 18.8, 17.1. **FTIR** (thin film) cm^{-1}: 2925, 1701, 1366, 1259, 1164, 1091. **HRMS** (ESI) (*m/z*) calc'd for $C_{15}H_{27}N_4O_3$ $[M+H]^+$: 333.1897, found 333.1896. **TLC** (25% EtOAc in hexanes), R_f: 0.58 (anis).



Ketone 87: A solution of freshly prepared LDA in THF/hexanes (1.00 M, 180 µL, 0.180 mmol, 1.50 equiv) was added dropwise via syringe to a stirred solution of hydrazone **86**[61] (51.6 mg, 0.180 mmol, 1.50 equiv) in THF (300 µL) at –78 °C, which was subsequently allowed to warm to 0 °C. After 1 h, the stirred reaction mixture was cooled to –78 °C before HMPA (70 µL) was added dropwise via syringe. After an additional 1 h, a solution of iodide **78** (52.4 mg, 0.120 mmol, 1.00 equiv) in THF (100 µL) was added dropwise via syringe to the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 100 µL). After 3 h, the stirred reaction mixture was allowed to warm to ambient temperature before water (10 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with water (4 × 10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford crude hydrazone **S5**, which was used without further purification.

Silica gel (0.45 g) was added in a single portion to a stirred solution of crude hydrazone **S5** in CH_2Cl_2 (2.5 mL). After 12 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% EtOAc in hexanes) to afford ketone **87** (27 mg, 41%). **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.05 (br. s., 1H), 3.72 (dd, *J* = 3.1, 12.5 Hz, 1H), 3.64–3.53 (m, 3H), 3.30 (d, *J* = 7.1 Hz, 1H), 2.89 (dd, *J* = 8.6, 12.2 Hz, 1H), 2.27 (dt, *J* = 7.2, 13.2 Hz, 1H), 2.16 (dd, *J* = 5.8, 16.4 Hz, 1H), 2.12–2.06 (m, 2H), 2.04–1.92 (m, 2H), 1.78 (s, 3H), 1.82–1.72 (m, 2H), 1.68 (br. s., 1H), 1.57–1.49 (m, 1H), 1.44 (s, 9H), 1.43–1.24 (m, 5H), 1.09 (tdd, *J* = 2.3, 4.5, 13.1 Hz, 1H), 1.00 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H),

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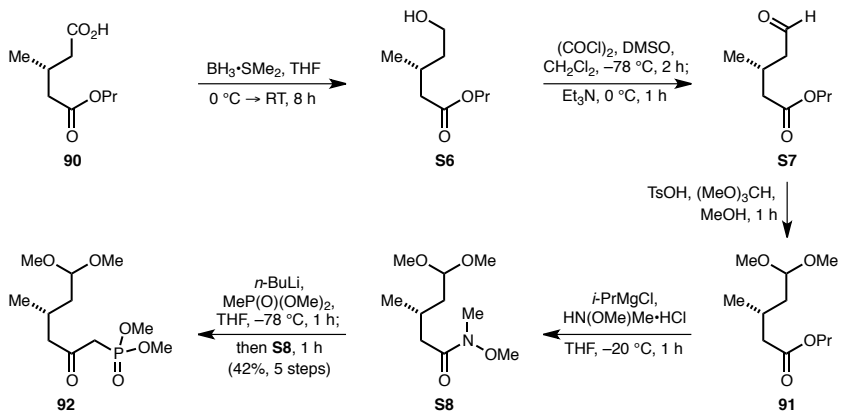
[61] For brevity, the synthesis of known hydrazone **86** is not shown. For a procedure for the preparation of **86**, see ref. 13.

0.09 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ: 208.5, 152.6, 95.5, 80.0, 69.1, 61.7, 56.4, 53.4, 50.5, 45.7, 41.6, 40.3, 38.6, 30.6, 28.8, 26.6, 26.5, 25.5, 24.1, 20.5, 18.8, 18.7, –4.81, –4.84. **HRMS** (ESI) (*m/z*) calc'd for $C_{28}H_{53}N_4O_5Si$ $[M+H]^+$: 553.3780, found 533.3786. **TLC** (25% EtOAc in hexanes), R_f: 0.35 (anis).



β-Ketophosphonate 92: Borane dimethyl sulfide complex (2.75 mL, 27.5 mmol, 1.02 equiv) was added dropwise via syringe to a stirred solution of carboxylic acid **90**[62] (5.08 g, 27.0 mmol, 1.00 equiv) in THF (70 mL) at 0 °C, which was subsequently allowed to warm to ambient temperature. After 4 h, an additional portion of borane dimethyl sulfide complex (135 µL, 1.35 mmol, 0.05 equiv) was added dropwise via syringe to the stirred reaction mixture. After an additional 3 h, an additional portion of borane dimethyl sulfide complex (135 µL, 1.35 mmol, 0.05 equiv) was added dropwise via syringe to the stirred reaction mixture. After an additional 1 h, the stirred reaction mixture was cooled to 0 °C before water (20 mL) was added. The resultant mixture was vigorously stirred and allowed to warm to ambient temperature. The solution was partially concentrated under reduced pressure to remove most of the THF, and was then partitioned with Et_2O (500 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude alcohol **S6**, which was used without further purification.

Oxalyl chloride (4.57 mL, 54.0 mmol, 2.00 equiv) was added dropwise via syringe to a stirred solution of DMSO (4.80 mL, 67.5 mmol, 2.50 equiv) in CH_2Cl_2 (220 mL) at –78 °C. After 30

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[62] Prepared in one step from 3-methylglutaric anhydride according to the procedure in: Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A. *Org. Lett.* **2011**, *13*, 3758–3761. The enantiopurity of **90** was determined to be 93% ee by chiral HPLC using authentic (±)-**90** with kind assistance from Dr. P. Bindschädler.

min, a solution of crude alcohol **S6** in CH_2Cl_2 (50 mL) was added via cannula down the flask wall into the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of CH_2Cl_2 (2 × 5 mL). After 2 h, Et_3N (26.3 mL, 189 mmol, 7.00 equiv) was added down the flask wall into the stirred reaction mixture, which after 20 min was allowed to warm to 0 °C. After an additional 1 h at 0 °C, water (270 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude aldehyde **S7**, which was used without further purification.

p-Toluenesulfonic acid monohydrate (205 mg, 1.08 mmol, 0.040 equiv) was added in a single portion to a stirred solution of crude aldehyde **S7** and trimethyl orthoformate (8.86 mL, 81.0 mmol, 3.00 equiv) in MeOH (270 mL). After 1 h, a saturated aqueous $NaHCO_3$ solution (200 mL) was added to the stirred reaction mixture. After 15 min, the stirred reaction mixture was partitioned with Et_2O (600 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (100 mL) and EtOAc (2 × 100 mL). The combined organic layers were then washed with water (2 × 400 mL) and brine (400 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude dimethyl acetal **91**, which was used without further purification.

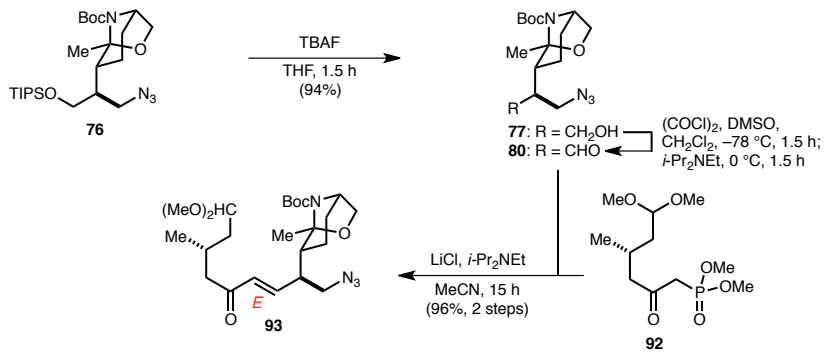
Batch 1. A solution of isopropylmagnesium chloride in THF (1.68 M, 5.36 mL, 9.00 mmol, 3.80 equiv) was added dropwise via syringe to a stirred solution of crude **91** (517 mg, 2.37 mmol, 1.00 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (468 mg, 5.35 mmol, 2.26 equiv) in THF (6 mL) at –20 °C. After 1 h, water (5 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant mixture was partitioned with Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude Weinreb amide **S8**.

Batch 2. A solution of isopropylmagnesium chloride in THF (1.68 M, 51.6 mL, 86.6 mmol, 3.80 equiv) was added dropwise via syringe to a stirred solution of crude **91** (4.98 g, 22.8 mmol, 1.00 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (4.45 g, 45.6 mmol, 2.00 equiv) in THF (46 mL) at –20 °C. After 1 h, water (50 mL) was added to the vigorously stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant mixture was partitioned with Et_2O (100 mL) and the layers were separated. The aqueous layer was extracted with 9:1 EtOAc/hexanes solution (3 × 50 mL), and the combined organic layers were washed with water (2 × 200 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was combined with material from batch 1, passed through a short plug of silica gel (Et_2O), and concentrated under reduced pressure to afford Weinreb amide **S8**, which was used without further purification.

A solution of *n*-butyllithium in hexanes (2.66 M, 29.3 mL, 75.0 mmol, 3.60 equiv) was added dropwise via syringe to a stirred solution of dimethyl methylphosphonate (8.67 mL, 80.0 mmol, 3.83 equiv) in THF (200 mL) at –78 °C. After 1 h, a solution of Weinreb amide **S8** (4.58 g, 20.9 mmol, 1.00 equiv) in THF (40 mL) was added dropwise via cannula to the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 5 mL). After 1 h, a saturated aqueous NH_4Cl solution (250 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. Et_2O (300 mL) was added to resultant mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with water (3 × 500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (~3.5 g)[63] was purified by flash column chromatography (silica gel, eluent: gradient, 0% → 2% → 10% MeOH in EtOAc) to afford β-ketophosphonate **92** (3.17 g, 42%) as a tan oil. **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.40 (dd, *J* =

[63] The unexpected poor mass recovery may be in part due to partial water solubility of **92**.

5.0, 6.6 Hz, 1H), 3.39 (d, *J* = 2.3 Hz, 3H), 3.37 (d, *J* = 2.3 Hz, 3H), 3.15 (s, 3H), 3.12 (s, 3H), 2.82–2.70 (m, 2H), 2.51–2.43 (m, 1H), 2.33–2.22 (m, 2H), 1.66 (td, *J* = 6.3, 14.0 Hz, 1H), 1.42 (ddd, *J* = 4.8, 7.3, 14.0 Hz, 1H), 0.89 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 201.0 (d, *J* = 6.0 Hz), 103.5, 52.71 (d, *J* = 5.0 Hz), 52.67 (d, *J* = 5.0 Hz), 52.2, 51.5 (d, *J* = 0.9 Hz), 42.4 (d, *J* = 126 Hz), 39.6, 25.8, 20.7. **FTIR** (thin film) cm^{-1}: 2955, 1712, 1256, 1124, 1021, 803. **HRMS** (ESI) (*m/z*) calc'd for $C_{11}H_{23}NaO_6P$ $[M+Na]^+$: 305.1125, found 305.1126. **TLC** (5% MeOH in CH_2Cl_2), R_f: 0.29 (anis).



Enone 93: A solution of TBAF in THF (1.0 M, 7.1 mL, 7.1 mmol, 1.2 equiv) was added to a stirred solution of bicyclic aminal **76** (2.85 g, 5.90 mmol, 1.00 equiv) in THF (59 mL). After 1.5 h, brine (100 mL) and Et_2O (100 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 20% → 25% EtOAc in hexanes) to afford alcohol **77** (1.81 g, 94%) as a colorless oil, which was used directly in the next reaction.

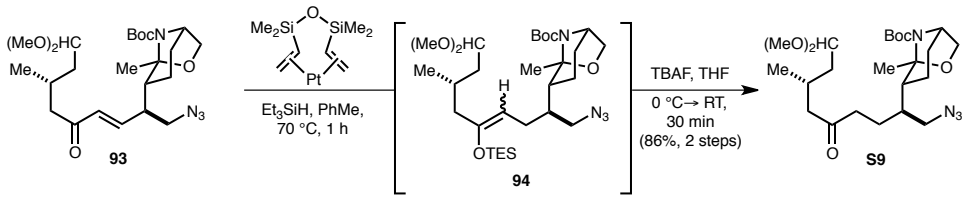
DMSO (1.97 mL, 27.8 mmol, 5.00 equiv) was added dropwise via syringe to a stirred solution of oxalyl chloride (940 µL, 11.1 mmol, 2.00 equiv) in CH_2Cl_2 (40 mL) at –78 °C. After 1 h, a solution of alcohol **77** (1.81 g, 5.55 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) was added via cannula down the flask wall into the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of CH_2Cl_2 (2 × 2.5 mL). After 1.5 h, diisopropylethylamine (9.70 mL, 55.5 mmol, 10.0 equiv) was added down the flask wall into the stirred reaction mixture, which after 5 min was allowed to warm to 0 °C. After an additional 1.5 h at 0 °C, aqueous HCl (1.2 M, 60 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (150 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 60 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl solution (2 × 200 mL), aqueous pH 7.5 phosphate buffer (0.1 M, 2 × 200 mL), and

brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude aldehyde **80**, which was used without further purification.

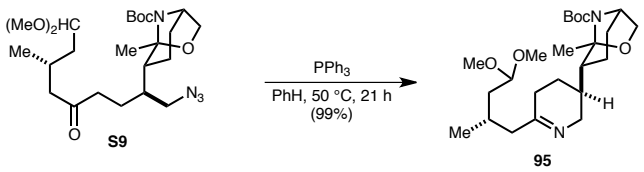
A round-bottom flask was charged with crude aldehyde **80** and β-ketophosphonate **92** (2.53 g, 9.70 mmol, 1.75 equiv), which were then azeotropically dried with three portions of benzene before MeCN (10 mL) was introduced via syringe. A separate round-bottom flask was charged with lithium chloride (705 mg, 16.6 mmol, 3.00 equiv). The flask was then flame-dried under vacuum (~0.1 torr), purged with argon, and allowed to cool to ambient temperature, and this process was repeated twice before MeCN (10 mL) was introduced into the flask via syringe. The aforementioned solution of crude aldehyde **80** and β-ketophosphonate **92** was then transferred via cannula to the stirred solution of lithium chloride in MeCN. The transfer was completed with three additional portions of MeCN (3 × 10 mL). Diisopropylethylamine (2.90 mL, 16.6 mmol, 3.00 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 15 h, saturated aqueous NH_4Cl solution (100 mL) and Et_2O (150 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 13% → 17% → 20% → 25% EtOAc in hexanes) to afford (*E*)-enone **93**[64] (2.55 g, 96%) as a colorless oil. **^{1}H NMR** (500 MHz, C_6D_6) δ: 6.68 (dd, *J* = 8.2, 15.8 Hz, 1H), 6.04 (d, *J* = 15.8 Hz, 1H), 4.43 (dd, *J* = 5.0, 6.6 Hz, 1H), 3.98 (br. s., 1H), 3.62–3.54 (m, 2H), 3.25 (d, *J* = 7.3 Hz, 1H), 3.17 (s, 3H), 3.14 (s, 3H), 2.96 (dd, *J* = 10.1, 12.6 Hz, 1H), 2.56–2.48 (m, 1H), 2.41–2.30 (m, 2H), 2.16–2.04 (m, 2H), 1.73 (s, 3H), 1.74–1.67 (m, 1H), 1.62–1.53 (m, 1H), 1.48–1.40 (m, 1H), 1.38 (s, 9H), 1.28–1.19 (m, 2H), 1.03 (tdd, *J* = 2.3, 4.3, 13.3 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 198.3, 152.4, 145.6, 132.3, 103.5,

[64] The olefin geometry was assigned as *E* by the 15.8 Hz value of the C11–H and C12–H coupling constant.

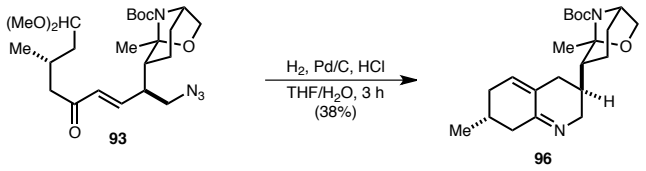
94.9, 80.2, 69.2, 56.3, 52.6, 52.2, 51.5, 48.7, 47.1, 43.6, 39.8, 28.8, 26.5, 24.3, 20.9, 20.2. **FTIR** (thin film) cm^{-1}: 2942, 1695, 1626, 1365, 1310, 1158, 1124, 1052, 863. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{41}N_4O_6$ $[M+H]^+$: 481.3021, found 481.3024. **TLC** (25% EtOAc in hexanes), R_f: 0.24 (anis).



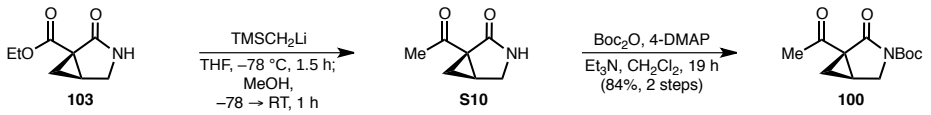
Ketone S9: A solution of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex in xylenes (2 wt. %, 6 drops) was added to a stirred solution of triethylsilane (330 µL, 2.07 mmol) in toluene (400 µL). This stock solution was stirred for 15 min, before an aliquot (367 µL, 1.04 mmol, 5.00 equiv) was removed and added to a stirred solution of enone **93** (96 mg, 0.21 mmol, 1.0 equiv) in toluene (300 µL). The resultant stirred reaction mixture was then heated to 70 °C. After 1 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was concentrated under reduced pressure to afford crude enol silyl ether **94**. THF (2 mL) was then introduced into the flask via syringe and the subsequent stirred solution was cooled to 0 °C. A solution of TBAF in THF (1.0 M, 300 µL, 0.30 mmol, 1.5 equiv) was added dropwise via syringe to the stirred reaction mixture at 0 °C, which was subsequently allowed to warm to ambient temperature. After 30 min, brine (5 mL) and Et_2O (5 mL) were added to the stirred reaction mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 13% → 20% EtOAc in hexanes) to afford ketone **S9** (83 mg, 86%). **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.44 (dd, *J* = 4.9, 6.8 Hz, 1H), 4.04 (br. s., 1H), 3.71 (dd, *J* = 3.1, 12.5 Hz, 1H), 3.61 (ddd, *J* = 1.5, 5.2, 7.0 Hz, 1H), 3.30 (d, *J* = 7.1 Hz, 1H), 3.19 (s, 3H), 3.15 (s, 3H), 2.89 (dd, *J* = 8.4, 12.2 Hz, 1H), 2.37–2.24 (m, 1H), 2.13 (dd, *J* = 6.2, 16.5 Hz, 1H), 2.09–2.03 (m, 2H), 2.03–1.96 (m, 1H), 1.92 (dd, *J* = 7.3, 16.7 Hz, 1H), 1.77 (s, 3H), 1.81–1.61 (m, 4H), 1.43 (s, 9H), 1.48–1.35 (m, 2H), 1.32–1.24 (m, 2H), 1.09 (tdd, *J* = 2.1, 4.3, 13.0 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 208.3, 152.6, 103.5, 95.5, 80.0, 69.1, 56.4, 53.4, 52.7, 52.2, 50.3, 45.7, 41.5, 39.8, 38.6, 28.8, 26.0, 25.4, 24.1, 20.9, 18.7. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{43}N_4O_6$ $[M+H]^+$: 483.3177, found 483.3188. **TLC** (25% EtOAc in hexanes), R_f: 0.29 (anis).



Imine 95: Triphenylphosphine on a polystyrene solid support (~3.0 mmol/g, 133 mg, 0.400 mmol, 3.00 equiv) was added in a single portion to a stirred solution of ketone **S9** (0.064 g, 0.133 mmol, 1.00 equiv) in benzene (3 mL), which was subsequently warmed to 50 °C. After 21 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was filtered through a pad of Celite. The Celite pad was washed with 10 mL of EtOAc, and the resultant mixture was concentrated under reduced pressure to afford analytically pure imine **95** (57.2 mg, 99%). **^{1}H NMR** (600 MHz, C_6D_6) δ: 4.55 (dd, *J* = 5.0, 6.7 Hz, 1H), 4.20 (d, *J* = 17.3 Hz, 1H), 4.06 (br. s., 1H), 3.66 (ddd, *J* = 1.6, 5.2, 7.0 Hz, 1H), 3.53–3.45 (m, 1H), 3.34 (d, *J* = 7.0 Hz, 1H), 3.21 (s, 3H), 3.18 (s, 3H), 2.29 (sxtd, *J* = 6.8, 13.8 Hz, 1H), 2.16 (dd, *J* = 6.6, 14.5 Hz, 1H), 2.01 (s, 3H), 1.92–1.88 (m, 1H), 1.85 (s, 3H), 1.88–1.83 (m, 1H), 1.83–1.69 (m, 3H), 1.51 (ddd, *J* = 5.0, 8.4, 13.8 Hz, 1H), 1.48–1.42 (m, 9H), 1.48–1.42 (m, 1H), 1.23 (td, *J* = 5.2, 13.5 Hz, 1H), 1.19–1.10 (m, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 167.5, 152.6, 103.7, 95.6, 79.7, 69.1, 56.4, 52.7, 52.2, 51.0, 48.5, 47.7, 40.1, 34.1, 31.9, 28.8, 27.5, 25.4, 24.0, 20.9, 18.9. **FTIR** (thin film) cm^{-1}: 2938, 1694, 1366, 1162, 1126, 1076. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{42}N_2NaO_5$ $[M+Na]^+$: 461.2986, found 461.2997. **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.45 (ninhydrin).



α,β-Unsaturated imine 96: Palladium on carbon (5 wt. %, 0.078 g, 0.037 mmol, 0.100 equiv) was added in one portion to a stirred solution of enone **93** (0.176 g, 0.370 mmol, 1.00 equiv) and aqueous HCl (1.2 M, 4.0 mL) in THF (32 mL). The stirred reaction mixture was then placed under a balloon of hydrogen. After 3 h, the hydrogen balloon was removed, and the stirred reaction mixture was sparged with argon for 5 min before saturated aqueous $NaHCO_3$ solution (5 mL) and Et_2O (10 mL) were added. The reaction mixture was filtered through a pad of Celite, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude air-sensitive α,β-unsaturated imine **96** (52 mg, 38%) as a white foam, which was unstable to flash column chromatography and prolonged storage. **^{1}H NMR** (500 MHz, C_6D_6) δ: 5.52 (dd, *J* = 2.3, 5.0 Hz, 1H), 4.39 (d, *J* = 16.6 Hz, 1H), 4.10–3.99 (m, 1H), 3.65 (ddd, *J* = 1.6, 5.2, 7.1 Hz, 1H), 3.53 (dd, *J* = 9.0, 18.1 Hz, 1H), 3.32 (d, *J* = 7.3 Hz, 1H), 2.82–2.72 (m, 1H), 2.15 (t, *J* = 13.3 Hz, 1H), 1.81 (br. s., 3H), 2.09–1.68 (m, 5H), 1.66–1.57 (m, 1H), 1.52–1.34 (m, 3H), 1.43 (s, 9H), 1.26 (td, *J* = 5.5, 12.5 Hz, 1H), 1.12 (tdd, *J* = 1.7, 5.9, 12.9 Hz, 1H), 0.82 (d, *J* = 6.6 Hz, 1H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 163.8, 152.6, 132.2, 130.9, 95.7, 79.7, 69.2, 56.4, 52.0, 47.3, 43.5, 35.0, 34.8, 33.7, 30.6, 30.3, 28.8, 24.1, 21.5, 19.4. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{35}N_2O_3$ $[M+H]^+$: 375.2642, found 375.2656. **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.40 (ninhydrin).



Methyl ketone 100: A solution of trimethylsilylmethyllithium in pentane (0.71 M, 20 mL, 14 mmol, 4.0 equiv) was added dropwise via syringe pump over 30 min to a solution of ethylester **103**[65] (0.600 g, 3.55 mmol, 1.00 equiv) in THF (17.7 mL) at –78 °C. After the addition was completed, the reaction mixture was stirred for an additional 1 h at –78 °C before MeOH (6 mL) was added. The reaction mixture was subsequently allowed to warm to ambient temperature and was stirred for an additional 1 h before brine (7 mL) was added. The resultant solution was partially concentrated under reduced pressure to remove THF, and the resultant mixture was extracted with CH_2Cl_2 (8 × 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to afford crude methyl ketone **S10**, which was used without further purification.

Di-*tert*-butyl dicarbonate (1.01 g, 4.65 mmol, 1.40 equiv) was added in one portion to a stirred solution of crude **S10** (462 mg, 3.32 mmol, 1.00 equiv), 4-dimethylaminopyridine (40.6 mg, 0.332 mmol, 0.100 equiv), and Et_3N (1.40 mL, 10.0 mmol, 3.00 equiv) in CH_2Cl_2 (16 mL). After 19 h, the reaction mixture was concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel, eluent: gradient, 20% → 33% EtOAc in hexanes) to afford methyl ketone **100** (714 mg, 84%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 3.78 (dd, *J* = 5.7, 11.3 Hz, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), 2.58 (s, 3H), 2.45 (td, *J* = 5.6, 7.9 Hz, 1H), 1.98 (dd, *J* = 4.1, 7.9 Hz, 1H), 1.52 (s, 9H), 1.29 (dd, *J* = 4.2, 5.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 201.8, 170.0, 150.2, 83.4, 46.1, 40.0, 29.7, 28.0, 24.4, 24.2. **FTIR** (thin film) cm^{-1}: 2979, 1779, 1744, 1694, 1366, 1303, 1255, 1148, 971, 851, 781. **HRMS** (ESI) (*m/z*) calc'd for $C_{12}H_{17}NNaO_4$ $[M+Na]^+$: 262.1050, found 262.1051. **TLC** (25% EtOAc in hexanes), R_f: 0.25 (anis).

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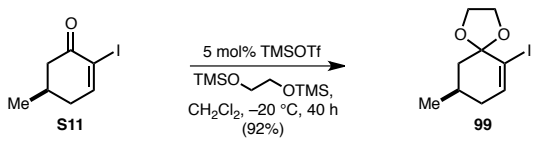
[65] Prepared from (*S*)-epichlorohydrin in four steps on multigram scale following a modified literature procedure: Medda, A. K.; Lee, H.-S. *Synlett* **2009**, *6*, 921–924.



(–)-(*R*)-5-methyl-2-iodo-2-cyclohexen-1-one ethylene ketal (99): TMSOTf (0.200 mL, 1.11 mmol, 0.050 equiv) was added dropwise via syringe to a stirred solution of 1,2-bis(trimethylsilyloxy)ethane (6.52 mL, 26.6 mmol, 1.20 equiv) and **S11**[66] (5.23 g, 22.2 mmol, 1.00 equiv) in CH_2Cl_2 (37 mL) at –78 °C. The resultant reaction mixture was then allowed to warm to –20 °C. After 40 h, Et_3N (750 µL) was added via syringe to the reaction mixture at –78 °C, which was subsequently allowed to warm to room temperature. The resultant mixture was then concentrated under reduced pressure and the residue directly purified by flash column chromatography (silica gel treated with 1% Et_3N in [5% EtOAc in hexanes], eluent: 1% Et_3N in [5% EtOAc in hexanes]) to afford vinyl iodide (–)-**99** (5.72 g, 92%) as a white solid and **S11** (0.140 g, 3%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 6.64 (dd, *J* = 2.3, 5.9 Hz, 1H), 4.26–4.16 (m, 2H), 4.02 (dt, *J* = 4.1, 6.6 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 1H), 2.12 (ddd, *J* = 2.1, 4.1, 17.6 Hz, 1H), 2.06–2.01 (m, 1H), 1.99 (dd, *J* = 2.6, 12.9 Hz, 1H), 1.76 (ddd, *J* = 2.3, 10.6, 17.8 Hz, 1H), 1.59 (t, *J* = 12.9 Hz, 1H), 0.97 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 144.1, 106.8, 103.2, 66.0, 65.3, 42.6, 37.6, 27.4, 21.0. **FTIR** (thin film) cm^{-1}: 2953, 1325, 1148, 1060, 972. **HRMS** (ESI) (*m/z*) calc'd for $C_9H_{14}IO_2$ $[M+H]^+$: 281.0033, found 281.0047. **$[\alpha]_D^{24}$**: –103 (*c* = 1.0, $CHCl_3$). **TLC** (17% EtOAc in hexanes), R_f: 0.62 (UV, anis).

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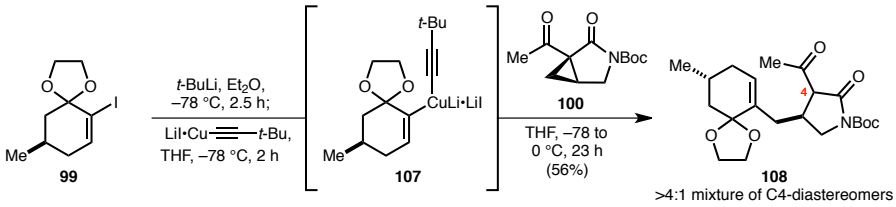
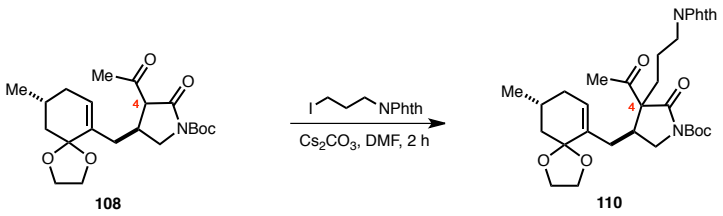
[66] Prepared from (*R*)-pulegone in 5 steps on multigram scale following literature protocols: Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673 and references therein.

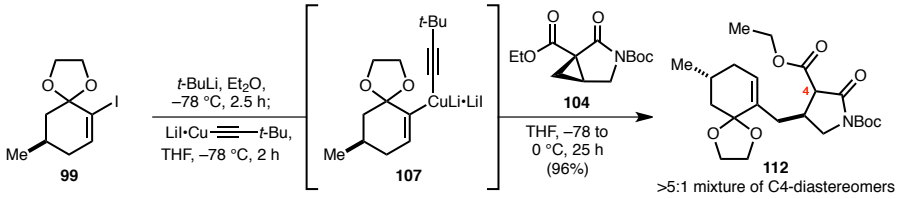


β-Ketoimide 108: A round-bottom flask was charged with vinyl iodide **99** (177 mg, 0.630 mmol, 1.50 equiv) and azeotropically dried with three portions of benzene. Et_2O (1 mL) was then introduced, and the resultant solution was cooled to –78 °C. A solution of *t*-butyllithium in pentane (1.61 M, 780 µL, 1.25 mmol, 3.00 equiv) was then added dropwise via syringe over 10 min to the stirred solution at –78 °C. The reaction mixture was stirred for an additional 1.5 h at –78 °C. A separate pear-shaped flask was charged with 3,3-dimethyl-1-butyne (78.0 µL, 0.630 mmol, 1.50 equiv) and THF (100 µL) and cooled to 0 °C. A solution of *n*-butyllithium in hexanes (2.50 M, 252 µL, 0.630 mmol, 1.50 equiv) was added dropwise to the stirred solution at 0 °C. After 10 min, the resultant homogeneous solution was added dropwise via cannula into a stirred slurry of copper(I) iodide (120 mg, 0.630 mmol, 1.50 equiv) in THF (200 µL) at 0 °C. The transfer was completed with two additional portions of THF (2 × 200 µL). After 1 h, the resultant red solution of copper acetylide at 0 °C was added dropwise via cannula over 20 min to the vigorously stirred heterogeneous solution of vinyl lithium at –78 °C. The transfer was completed with two additional portions of THF (2 × 250 µL). After 2 h, a cooled solution of methyl ketone **100** (100 mg, 0.420 mmol, 1.00 equiv), which was azeotropically dried with three portions of benzene, in THF (250 µL) was added dropwise via syringe to the vigorously stirred off-white reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 125 µL). The reaction mixture was allowed to gradually warm to 0 °C over 3 h, during which time it became orange in color. After 23 h, a saturated aqueous NH_4Cl solution (1 mL) was added to the stirred reaction mixture at 0 °C, which was allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (10 mL), and the layers were separated. The organic phase was extracted with a 9:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (3 × 5 mL). The combined aqueous layers were extracted

with Et_2O (4 × 5 mL). The combined organic layers were washed with a 9:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (2 × 25 mL), water (25 mL), and brine (25 mL). The organic layers were then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel treated with 1% Et_3N in CH_2Cl_2, eluent: gradient, 1% Et_3N in [0% EtOAc in CH_2Cl_2] → 1% Et_3N in [10% EtOAc in CH_2Cl_2]) to afford β-ketoimide **108** (93 mg, 56%) as a >4:1 mixture of C4-epimers. **^{1}H NMR** (500 MHz, $CDCl_3$, >4:1 mixture of epimers; major C4-epimer reported) δ: 5.70 (d, *J* = 5.0 Hz, 1H), 4.07–4.01 (m, 2H), 4.00–3.88 (m, 2H), 3.83 (dd, *J* = 8.0, 10.8 Hz, 1H), 3.41 (d, *J* = 7.8 Hz, 1H), 3.28 (dd, *J* = 6.9, 10.8 Hz, 1H), 3.00 (qd, *J* = 7.7, 15.3 Hz, 1H), 2.36 (s, 3H), 2.19 (dd, *J* = 7.1, 14.0 Hz, 1H), 2.10 (td, *J* = 4.9, 17.7 Hz, 1H), 2.04 (dd, *J* = 8.5, 14.2 Hz, 1H), 1.90–1.78 (m, 2 H), 1.62 (dd, *J* = 9.2, 17.9 Hz, 1H), 1.50 (s, 9H), 1.27 (t, *J* = 13.2 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, >4:1 mixture of epimers; major C4-epimer reported) δ: 202.1, 169.2, 150.0, 134.1, 131.9, 107.9, 83.3, 65.3, 64.1, 63.1, 49.9, 41.9, 33.9, 33.6, 31.7, 30.4, 27.9, 27.4, 21.4. **FTIR** (thin film) cm^{-1}: 2929, 1781, 1715, 1677, 1368, 1307, 1254, 1151, 967, 850. **HRMS** (ESI) (*m/z*) calc'd for $C_{21}H_{31}NNaO_6$ $[M+Na]^+$: 416.2044, found 416.2043. **TLC** (33% EtOAc in hexanes), R_f: 0.35 (anis).



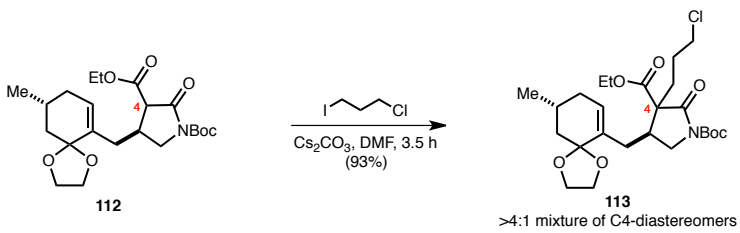
Representative Example of Alkylation of β-Ketoimide 108: Cesium carbonate (16.6 mg, 0.051 mmol, 2.00 equiv) was added in a single portion to a vigorously stirred solution of β-ketoimide **108** (10 mg, 0.025 mmol, 1.0 equiv) and *N*-(3-iodopropyl)phthalimide (16.1 mg, 0.051 mmol, 2.00 equiv) in DMF (200 µL). After 2 h, Et_2O (5 mL) and saturated aqueous NH_4Cl solution (5 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with water (4 × 20 mL) and brine (20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude residue showed an ~1:1 ratio of desired *C*-alkylated phthalimide **110** to a mixture of byproducts, which are tentatively assigned as products corresponding to *O*-alkylation. An analytical sample of **110**, as a single C4-diastereomer, was obtained by flash column chromatography (silica gel, eluent: 17% EtOAc in hexanes). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.84–7.82 (m, 2H), 7.74–7.70 (m, 2H), 5.68 (d, *J* = 4.4 Hz, 1H), 4.06–3.99 (m, 2H), 3.92–3.86 (m, 2H), 3.79–3.71 (m, 2H), 3.67 (td, *J* = 7.0, 13.5 Hz, 1H), 3.39 (t, *J* = 10.3 Hz, 1H), 2.62–2.54 (m, 1H), 2.38 (dd, *J* = 3.4, 14.2 Hz, 1H), 2.19 (s, 3H), 2.17–2.04 (m, 2H), 1.85–1.79 (m, 3H), 1.73 (d, *J* = 13.2 Hz, 1H), 1.64–1.55 (m, 2H), 1.52 (s, 9H), 1.27–1.13 (m, 2H), 0.90 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 206.1, 172.5, 168.3, 150.1, 133.9, 133.9, 132.2, 132.1, 123.2, 108.1, 83.2, 65.9, 65.4, 64.0, 49.4, 41.7, 38.1, 37.7, 34.0, 29.8, 29.7, 29.3, 28.0, 27.4, 23.8, 21.4. **FTIR** (thin film) cm^{-1}: 2926, 1772, 1711, 1436, 1396, 1367, 1154, 967, 721. **HRMS** (ESI) (*m/z*) calc'd for $C_{32}H_{40}N_2NaO_8$ $[M+Na]^+$: 603.2677, found 603.2685. **TLC** (33% EtOAc in hexanes), R_f: 0.62 ($KMnO_4$).



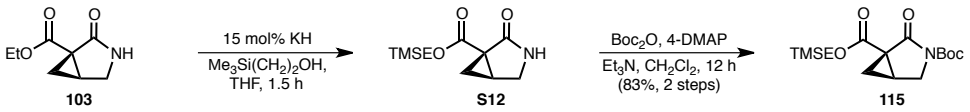
β-Carboethoxyimide 112: A round-bottom flask was charged with vinyl iodide **99** (390 mg, 1.39 mmol, 1.50 equiv) and azeotropically dried with three portions of benzene. Et_2O (2.2 mL) was then introduced, and the resultant solution was cooled to –78 °C. A solution of *t*-butyllithium in pentane (1.58 M, 1.77 mL, 2.79 mmol, 3.00 equiv) was then added dropwise via syringe over 10 min to the stirred solution at –78 °C. The reaction mixture was stirred for an additional 1.5 h at –78 °C. A separate pear-shaped flask was charged with 3,3-dimethyl-1-butyne (172 µL, 1.39 mmol, 1.50 equiv) and THF (500 µL) and cooled to 0 °C. A solution of *n*-butyllithium in hexanes (2.38 M, 585 µL, 1.39 mmol, 1.50 equiv) was added dropwise to the stirred solution at 0 °C. After 10 min, the resultant homogeneous solution was added dropwise via syringe into a stirred slurry of copper(I) iodide (266 mg, 1.39 mmol, 1.50 equiv) in THF (500 µL) at 0 °C. The transfer was completed with two additional portions of THF (2 × 250 µL). After 1 h, the resultant red solution of copper acetylide at 0 °C was added dropwise via cannula over 20 min to the vigorously stirred heterogeneous solution of vinyl lithium at –78 °C. The transfer was completed with two additional portions of THF (2 × 500 µL). After 1.5 h, a cooled solution of ethylester **104**[67] (250 mg, 0.928 mmol, 1.00 equiv), which was azeotropically dried with three portions of benzene, in THF (500 µL) at –78 °C was added dropwise via cannula to the vigorously stirred off-white reaction mixture. The transfer was completed with two additional portions of THF (2 × 500 µL). The reaction mixture was allowed to gradually warm to 0 °C over 1 h, during which time it became orange in color. After 25 h, a saturated aqueous NH_4Cl solution (3 mL) was added to the reaction mixture at 0 °C, which was allowed to warm to ambient

[67] Pyrrolidinone **103** was *N*-Boc protected to afford ethylester **104** in quantitative yield following the same procedure used to *N*-Boc protect methyl ketone **100**.

temperature. The resultant mixture was diluted with Et_2O (20 mL), and the layers were separated. The organic phase was extracted with a 9:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (3 × 20 mL). The combined aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with a 9:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (4 × 50 mL) and brine (50 mL). The organic layers were then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel treated with 1% Et_3N in [17% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [17% EtOAc in hexanes] → 1% Et_3N in [25% EtOAc in CH_2Cl_2]) to afford β-carboethoxyimide **112** (378 mg, 96%) as a >5:1 mixture of C4-epimers. **^{1}H NMR** (500 MHz, $CDCl_3$, >5:1 mixture of epimers; major C4-epimer reported) δ: 5.72 (d, *J* = 3.4 Hz, 1H), 4.25–4.14 (m, 2H), 4.07–3.99 (m, 2H), 3.96–3.86 (m, 3H), 3.26 (dd, *J* = 7.9, 10.9 Hz, 1H), 3.22 (d, *J* = 9.2 Hz, 1H), 3.00–2.91 (m, 1H), 2.31 (dd, *J* = 6.4, 14.2 Hz, 1H), 2.11 (td, *J* = 4.5, 17.6 Hz, 1H), 2.05 (dd, *J* = 8.7, 14.0 Hz, 1H), 1.92–1.82 (m, 1H), 1.81 (td, *J* = 1.4, 12.9 Hz, 1H), 1.61 (ddd, *J* = 1.4, 10.8, 17.8 Hz, 1H), 1.51 (s, 9H), 1.31–1.23 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$, >5:1 mixture of epimers; major C4-epimer reported) δ: 168.6, 168.4, 150.0, 133.9, 131.8, 107.9, 83.2, 65.4, 64.1, 61.6, 56.7, 50.1, 41.8, 34.4, 33.9, 33.9, 28.0, 27.4, 21.4, 14.1. **FTIR** (thin film) cm^{-1}: 2924, 1788, 1757, 1720, 1369, 1306, 1256, 1154, 1045, 966, 850. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{33}NNaO_7$ $[M+Na]^+$: 446.2149, found 446.2152. **TLC** (33% EtOAc in hexanes), R_f: 0.42 (anis).

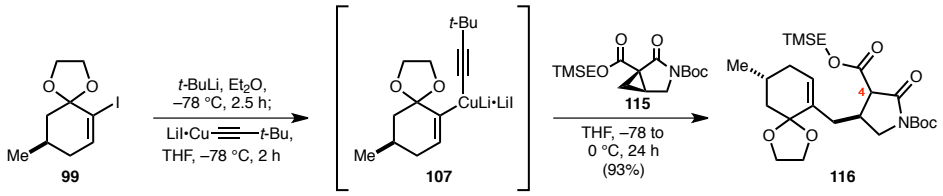


Alkyl chloride 113: 1-Chloro-3-iodopropane (192 µL, 1.79 mmol, 2.00 equiv) was added dropwise to a vigorously stirred solution of cesium carbonate (583 mg, 1.79 mmol, 2.00 equiv) and **112** (378 mg, 0.890 mmol, 1.00 equiv) in DMF (5 mL). After 3 h, Et_2O (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (4 × 30 mL) and brine (30 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel treated with 1% Et_3N, eluent: 1% Et_3N in [17% EtOAc in hexanes]) to afford alkyl chloride **113** (414 mg, 93%) as a >4:1 mixture of C4-epimers. **^{1}H NMR** (500 MHz, $CDCl_3$, >4:1 mixture of epimers; major C4-epimer reported) δ: 5.75 (dd, *J* = 1.8, 5.2 Hz, 1H), 4.26 (dd, *J* = 7.2, 10.9 Hz, 1H), 4.17–4.07 (m, 2H), 4.04–3.90 (m, 3H), 3.82 (dd, *J* = 8.1, 10.5 Hz, 1H), 3.62–3.50 (m, 2H), 3.36 (t, *J* = 10.4 Hz, 1H), 2.63–2.54 (m, 1H), 2.46 (d, *J* = 13.9 Hz, 1H), 2.12 (td, *J* = 5.0, 17.6 Hz, 1H), 2.07–1.79 (m, 4H), 1.75 (dd, *J* = 11.1, 14.0 Hz, 1H), 1.66 (dd, *J* = 10.5, 18.1 Hz, 1H), 1.54 (s, 9H), 1.30–1.25 (m, 4H), 0.96 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, >4:1 mixture of epimers; major C4-epimer reported) δ: 171.8, 169.3, 150.2, 133.5, 132.1, 108.1, 83.2, 65.3, 63.9, 61.5, 60.1, 49.5, 45.2, 41.6, 37.6, 34.0, 29.6, 29.3, 28.0, 27.9, 27.4, 27.3, 21.4, 14.2. **FTIR** (thin film) cm^{-1}: 2954, 1786, 1752, 1716, 1679, 1368, 1310, 1153, 1044, 966, 851, 777. **HRMS** (ESI) (*m/z*) calc'd for $C_{15}H_{26}IN_4O_3$ $[M+H]^+$: 437.1044, found 437.1046. **TLC** (33% EtOAc in hexanes), R_f: 0.25 (anis).



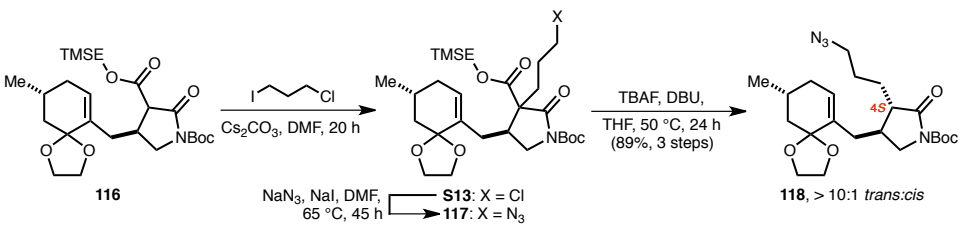
Cyclopropane 115: A solution of **103**[65] (2.54 g, 15.0 mmol, 1.00 equiv) in THF (25 mL) was added dropwise via cannula to a stirred solution of potassium hydride (90 mg, 2.25 mmol, 0.15 equiv) and 2-(trimethylsilyl)ethanol (21.5 mL, 150 mmol, 10.0 equiv) in THF (50 mL) at ambient temperature. The transfer was completed with two additional portions of THF (2 × 5 mL). After 1.5 h, brine (50 mL) and CH_2Cl_2 (300 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was then distilled via Kugelrohr (50 °C, ~1 torr) to remove excess 2-(trimethylsilyl)ethanol. Residual 2-(trimethylsilyl)ethanol was then removed by azeotropic distillation with three portions of toluene to yield crude **S12** (3.51 g) as a pale-yellow solid, which was used without further purification.

Di-*tert*-butyl dicarbonate (4.76 g, 21.8 mmol, 1.50 equiv) was added in one portion to a stirred solution of crude **S12** (3.51 g, 14.5 mmol, 1.00 equiv), 4-dimethylaminopyridine (0.178 g, 1.45 mmol, 0.100 equiv), and Et_3N (6.08 mL, 43.6 mmol, 3.00 equiv) in CH_2Cl_2 (75 mL) at 0 °C. The resultant reaction mixture was allowed to warm to ambient temperature. After 12 h, the reaction mixture was concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel, eluent: gradient, 17% → 20% EtOAc in hexanes) to afford cyclopropane (+)-**115** (4.27 g, 83%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.33–4.21 (m, 2H), 3.81 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 2.34 (td, *J* = 5.5, 8.1 Hz, 1H), 1.98 (dd, *J* = 4.6, 8.1 Hz, 1H), 1.50 (s, 9H), 1.27–1.23 (m, 1H), 1.11–1.01 (m, 2H), 0.03 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.7, 167.4, 150.3, 83.2, 64.2, 46.0, 32.8, 28.0, 22.0, 20.4, 17.4, –1.6. **FTIR** (thin film) cm^{-1}: 2955, 1791, 1761, 1715, 1308, 1157, 837. **HRMS** (ESI) (*m/z*) calc'd for $C_{16}H_{27}NNaO_5Si$ $[M+Na]^+$: 364.1551, found 364.1565. **$[\alpha]_D^{24}$**: +84 (*c* = 4.4, $CHCl_3$)). **TLC** (17% EtOAc in hexanes), R_f: 0.23 ($KMnO_4$).



β-Carbo-2-(trimethylsilyl)ethoxyimide 116: A round-bottom flask was charged with **99** (4.97 g, 17.7 mmol, 1.42 equiv) and azeotropically dried with four portions of benzene. Et_2O (36 mL) was then introduced, and the resultant solution was cooled to –78 °C. A solution of *t*-butyllithium in pentane (1.78 M, 19.9 mL, 35.5 mmol, 2.85 equiv) was then added dropwise over 20 minutes to the stirred solution at –78 °C. The reaction mixture was stirred for an additional 2.5 h at –78 °C. A separate pear-shaped flask was charged with 3,3-dimethyl-1-butyne (2.18 mL, 17.7 mmol, 1.42 equiv) and THF (6 mL) and cooled to 0 °C. A solution of *n*-butyllithium in hexanes (2.69 M, 6.60 mL, 17.7 mmol, 1.42 equiv) was added dropwise to the stirred solution at 0 °C. After 15 min, the resultant homogeneous solution was added via cannula into a stirred slurry of copper(I) iodide (3.38 g, 17.7 mmol, 1.42 equiv) in THF (6 mL) at 0 °C. The transfer was completed with two additional portions of THF (2 × 3 mL). After 1 h, the resultant red solution of copper acetylide at 0 °C was added via cannula dropwise over 20 minutes to the vigorously stirred heterogeneous solution of vinyl lithium at –78 °C. The transfer was completed with two additional portions of THF (2 × 9 mL). After 2 h, a cooled solution of **115** (4.27 g, 12.5 mmol, 1.00 equiv), which was dried by azeotroping with three portions of benzene, in THF (10 mL) at –78 °C was added via cannula dropwise to the vigorously stirred off-white reaction mixture. The transfer was completed with two additional portions of THF (2 × 5 mL). The reaction mixture was allowed to gradually warm to 0 °C over 3 h, during which time it became orange in color. After 24 h, a solution of saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture at 0 °C, which was allowed to warm to room temperature. The resultant mixture was diluted with Et_2O (200 mL), and the layers were separated. The organic phase was extracted with an 8:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (3 × 180 mL). The combined aqueous layers were extracted with Et_2O (4 × 200 mL).

The combined organic layers were washed with an 8:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) aqueous NH_4OH solution (2 × 180 mL), water (200 mL), and brine (200 mL). The organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel treated with 1% Et_3N in [9% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [9% EtOAc in hexanes] → 1% Et_3N in [14% EtOAc in hexanes]) to afford imide **116** (5.74 g, 93%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$, >10:1 mixture of epimers; major C4-epimer reported) δ: 5.73 (d, *J* = 4.1 Hz, 1H), 4.23 (ddd, *J* = 2.9, 6.8, 10.5 Hz, 2H), 4.08–4.00 (m, 2H), 3.97–3.88 (m, 3H), 3.27 (dd, *J* = 7.6, 10.8 Hz, 1H), 3.21 (d, *J* = 9.1 Hz, 1H), 2.96 (sxt, *J* = 8.0 Hz, 1H), 2.31 (dd, *J* = 5.6, 14.1 Hz, 1H), 2.12 (td, *J* = 5.1, 17.7 Hz, 1H), 2.05 (dd, *J* = 8.8, 14.1 Hz, 1H), 1.92–1.84 (m, 1H), 1.82 (dd, *J* = 1.5, 13.2 Hz, 1H), 1.62 (dd, *J* = 11.1, 17.3 Hz, 1H), 1.51 (s, 9H), 1.28 (t, *J* = 13.0 Hz, 1H), 1.07–1.00 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 168.7, 168.6, 150.1, 134.0, 131.7, 108.0, 83.2, 65.4, 64.1, 64.1, 56.9, 50.1, 41.9, 34.4, 34.0, 33.9, 28.0, 27.4, 21.4, 17.4, –1.6. **FTIR** (thin film) cm^{-1}: 2953, 1790, 1757, 1721, 1308, 1250, 1153, 837. **HRMS** (ESI) (*m/z*) calc'd for $C_{25}H_{41}NNaO_7Si$ $[M+Na]^+$: 518.2545, found 518.2513. **TLC** (33% EtOAc in hexanes), R_f: 0.53 (anis).



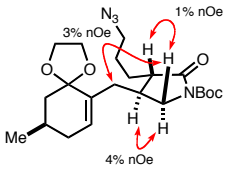
***N*-Boc-2-pyrrolidinone 118:** 1-Chloro-3-iodopropane (1.61 mL, 15.0 mmol, 1.30 equiv) was added dropwise to a vigorously stirred solution of cesium carbonate (7.49 g, 23.0 mmol, 2.00 equiv) and **116** (5.70 g, 11.5 mmol, 1.00 equiv) in DMF (38 mL). After 20 h, Et_2O (200 mL) and saturated aqueous NH_4Cl solution (100 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed with water (4 × 150 mL) and brine (150 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was azeotropically dried with five portions of toluene to remove residual 1-chloro-3-iodopropane and placed under reduced pressure for 36 h to afford crude alkyl chloride **S13** (6.87 g) as an off-white solid that used without further purification.

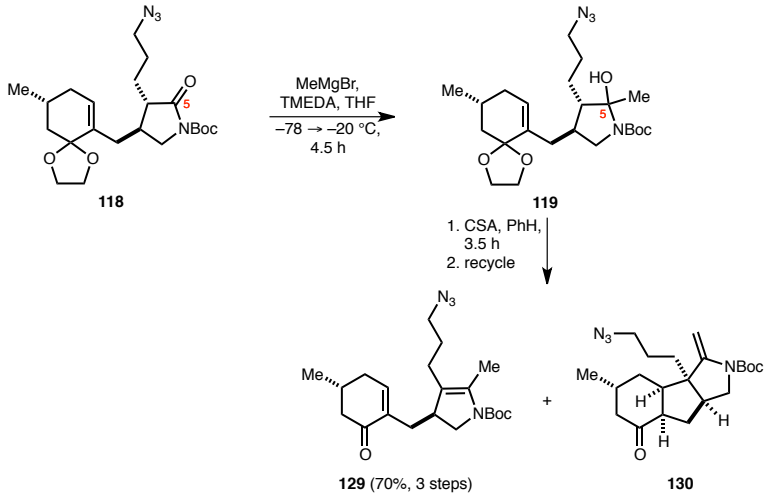
Sodium azide (2.24 g, 34.5 mmol, 3.00 equiv) and sodium iodide (1.72 g, 11.5 mmol, 1.00 equiv) were sequentially added to a vigorously stirred solution of crude **S13** (6.87 g, 11.5 mmol, 1.00 equiv) in DMF (46 mL), and the resultant reaction mixture was heated to 65 °C. After 45 h, the reaction mixture was cooled to ambient temperature before Et_2O (200 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and water (50 mL) were sequentially added. The layers were separated and the aqueous layer was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed with water (4 × 150 mL) and brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude alkyl azide **117** (6.53 g), which was used without further purification.

A solution of TBAF in THF (1.0 M, 11 mL, 11 mmol, 1.0 equiv) was added to a stirred solution of DBU (0.427 mL, 2.82 mmol, 0.250 equiv) and crude **117** (6.53 g, 11.3 mmol, 1.00 equiv) in THF (56 mL) at room temperature, and the resultant reaction mixture was heated to 50 °C. After 24 h, the reaction mixture was cooled to ambient temperature before Et_2O (150 mL) and water (150 mL)

were sequentially added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (silica gel treated with 1% Et_3N in [17% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [17% EtOAc in hexanes] → 1% Et_3N in [25% EtOAc in hexanes]) to afford *N*-Boc-2-pyrrolidinone **118** (4.43 g, 89%) as a white flocculent solid (>10:1 mixture of epimers at C4). **^{1}H NMR** (500 MHz, $CDCl_3$, >10:1 mixture of (4*S*)- and (4*R*)-epimers; major (4*S*)-epimer reported) δ: 5.73 (d, *J* = 3.7 Hz, 1H), 4.11–4.03 (m, 1H), 3.93 (s, 3H), 3.81 (dd, *J* = 7.6, 11.0 Hz, 1H), 3.32–3.26 (m, 2H), 3.20 (dd, *J* = 7.6, 11.0 Hz, 1H), 2.37 (dd, *J* = 5.4, 14.2 Hz, 1H), 2.29–2.09 (m, 3H), 1.99 (dd, *J* = 9.0, 14.2 Hz, 1H), 1.93–1.74 (m, 3H), 1.74–1.59 (m, 4H), 1.51 (s, 9H), 1.29 (t, *J* = 12.9 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, >10:1 mixture of C4-epimers; major (4*S*)-epimer reported) δ: 175.5, 150.4, 134.3, 131.4, 108.1, 82.8, 65.3, 64.0, 51.4, 50.2, 49.1, 41.8, 35.4, 34.2, 34.0, 28.0, 27.4, 26.5, 26.1, 21.4. **FTIR** (thin film) cm^{-1}: 2951, 2095, 1783, 1746, 1713, 1310, 1254, 1155, 966. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{34}KN_4O_5$ $[M+K]^+$: 473.2161, found 473.2148. **TLC** (33% EtOAc in hexanes), R_f: 0.40 (anis).

1D NOESY (500 MHz, $CDCl_3$):



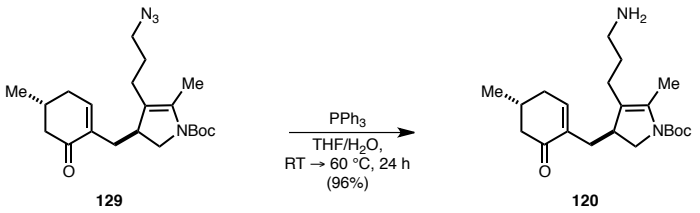


Dihydropyrrole 129: A solution of methylmagnesium bromide in Et_2O (3.0 M, 400 µL, 1.2 mmol, 3.0 equiv) was added dropwise via syringe to a stirred solution of *N*-Boc-2-pyrrolidinone **118** (172 mg, 0.400 mmol, 1.00 equiv) and TMEDA (232 µL, 2.00 mmol, 5.00 equiv) in THF (4 mL) at –78 °C. After 1 h, the resultant stirred reaction mixture was allowed to slowly warm to –20 °C over 2 h, whereupon the temperature was maintained at –20 °C. After an additional 1.5 h, the stirred solution was cooled to –78 °C before isopropanol (100 µL) and saturated aqueous NH_4Cl solution (5 mL) were added sequentially via syringe. The resultant mixture was then allowed to warm to ambient temperature before Et_2O (10 mL) and water (10 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude aminal **119**, which was used without further purification.

CSA (9.3 mg, 0.040 mmol, 0.10 equiv) was added in a single portion to a vigorously stirred solution of crude aminal **119** in benzene (8 mL). After 2 h, an additional portion of CSA (9.3 mg, 0.040 mmol, 0.10 equiv) was added to the vigorously stirred reaction mixture. After an additional 1 h, an additional portion of CSA (8.0 mg, 0.034 mmol, 0.090 equiv) was added to the vigorously stirred reaction mixture. After an additional 30 min, saturated aqueous $NaHCO_3$ solution (10 mL) was added to the stirred reaction mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$

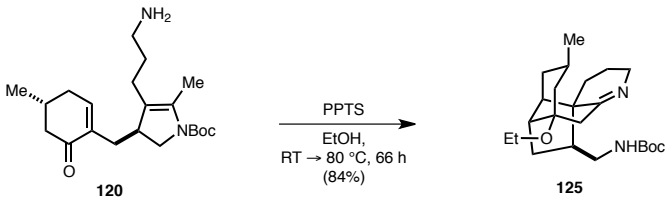
solution (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 8% → 50% EtOAc in hexanes) to afford dihydropyrrole **129** (95 mg) and a mixture of intermediate products (37 mg). The mixture of intermediate products was re-exposed to the aforementioned experimental procedure to give additional **129** (13 mg) after flash column chromatrography, which when combined with the previous material yielded **129** (108 mg, 70%). **^{1}H NMR** (500 MHz, C_6D_6, 70 °C) δ: 6.13 (dd, *J* = 2.1, 5.0 Hz, 1H), 3.62 (dd, *J* = 9.8, 11.5 Hz, 1H), 3.55 (dd, *J* = 4.9, 11.5 Hz, 1H), 2.89–2.77 (m, 2H), 2.88–2.77 (m, 1H), 2.74 (br. s., 1H), 2.62 (d, *J* = 13.7 Hz, 1H), 2.30 (d, *J* = 13.7 Hz, 1H), 2.10 (s, 3H), 2.04 (dd, *J* = 7.1, 14.6 Hz, 1H), 2.00–1.92 (m, 1H), 1.85–1.76 (m, 2H), 1.76–1.69 (m, 2H), 1.62–1.52 (m, 1H), 1.52–1.38 (m, 11H), 0.67 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6, 70 °C) δ: 198.0, 152.9, 144.8, 137.8, 135.0, 120.3, 79.8, 52.9, 51.5, 47.1, 41.0, 34.8, 34.1, 30.9, 29.0, 28.0, 23.2, 21.3, 13.6. **HRMS** (ESI) (*m/z*) calc'd for $C_{21}H_{33}N_4O_3$ $[M+H]^+$: 389.2547, found 389.2550. **TLC** (33% EtOAc in hexanes), R_f: 0.63 (anis).

Enamide **130** was characterized as a minor byproduct from this reaction. **^{1}H NMR** (500 MHz, C_6D_6) δ: 5.93 (br. s., 1H), 4.09 (s, 1H), 3.40–3.33 (m, 2H), 2.69–2.59 (m, 2H), 2.40 (q, *J* = 7.8 Hz, 1H), 2.14 (dd, *J* = 4.9, 14.2 Hz, 1H), 1.99–1.92 (m, 1H), 1.89 (q, *J* = 7.5 Hz, 1H), 1.84–1.70 (m, 3H), 1.54 (td, *J* = 7.8, 12.7 Hz, 1H), 1.46 (s, 9H), 1.41–1.28 (m, 3H), 1.21 (dt, *J* = 3.9, 12.9 Hz, 1H), 0.99 (dt, *J* = 3.9, 12.7 Hz, 1H), 0.94–0.83 (m, 1H), 0.73 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 210.4, 152.6, 147.9, 92.7, 80.6, 61.3, 54.9, 54.1, 52.1, 51.2, 46.1, 42.4, 38.4, 34.9, 31.7, 30.6, 28.7, 24.9, 20.6. **HRMS** (ESI) (*m/z*) calc'd for $C_{21}H_{32}N_4NaO_3$ $[M+Na]^+$: 411.2367, found 411.2344. **TLC** (33% EtOAc in hexanes), R_f: 0.57 (CAM).

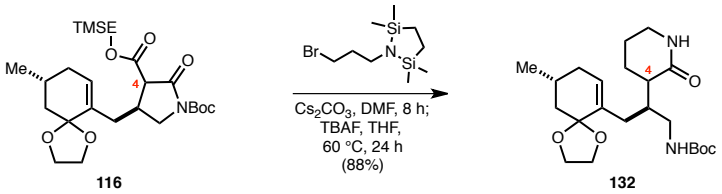


129 120

Primary amine 120: Triphenylphosphine (84 mg, 0.32 mmol, 1.5 equiv) was added in a single portion to a stirred solution of dihydropyrrole **129** (83 mg, 0.21 mmol, 1.0 equiv) in 8:1 THF/water (2.1 mL). After 1 h, the resultant stirred reaction mixture was heated to 60 °C. After an additional 14 h, the stirred reaction mixture was cooled to ambient temperature before additional triphenylphosphine (39 mg, 0.15 mmol, 0.71 equiv) was added in a single portion. The resultant stirred reaction mixture was subsequently heated to 60 °C. After an additional 9 h, the stirred reaction mixture was cooled to ambient temperature before the solvent was removed under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 1% Et_3N in CH_2Cl_2, eluent: gradient, 1% Et_3N in [2% MeOH in CH_2Cl_2] → 1% Et_3N in [8% MeOH in CH_2Cl_2]) to afford primary amine **120** (73 mg, 96%). **^{1}H NMR** (500 MHz, C_6D_6, 70 °C) δ: 6.16 (br. s., 1H), 3.66 (t, *J* = 9.8 Hz, 1H), 3.59 (dd, *J* = 4.9, 11.7 Hz, 1H), 2.85 (br. s., 1H), 2.72 (d, *J* = 13.4 Hz, 1H), 2.62–2.49 (m, 2H), 2.31 (d, *J* = 13.4 Hz, 1H), 2.15 (s, 3H), 2.20–2.11 (m, 1H), 2.10–2.03 (m, 1H), 1.87–1.70 (m, 4H), 1.63–1.53 (m, 1H), 1.47 (s, 9H), 1.53–1.42 (m, 2H), 1.25 (br. s., 2H), 0.67 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6, 70 °C) δ: 198.0, 153.0, 144.7, 137.9, 134.1, 121.9, 79.6, 52.9, 47.1, 42.4, 41.3, 34.9, 34.0, 32.9, 30.9, 29.1, 23.5, 21.3, 13.6. **HRMS** (ESI) (*m/z*) calc'd for $C_{21}H_{35}N_2O_3$ $[M+H]^+$: 363.2642, found 363.2640. **TLC** (18% MeOH and 2% NH_4OH in $CHCl_3$), R_f: 0.40 (ninhydrin).

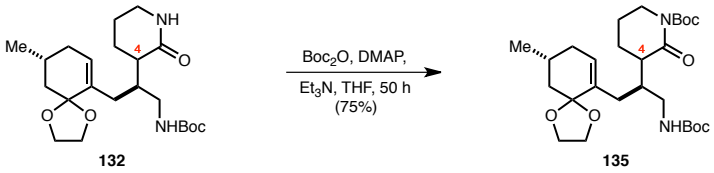


Tetracycle 125: A Schlenk tube was charged with primary amine **120** (25 mg, 0.069 mmol, 1.0 equiv), which was azeotropically dried with five portions of benzene. The reaction vessel was then further charged with pyridinium *p*-toluenesulfonic acid (3.5 mg, 0.014 mmol, 0.20 equiv) and ethanol (4 mL) and the resultant mixture was sparged with a stream of argon for 10 min. The tube was sealed, and heated to 60 °C. After 5 h, the stirred reaction mixture was further heated to 80 °C. After 61 h, the stirred solution was cooled to ambient temperature and concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 0.5% NH_4OH in [5% MeOH in $CHCl_3$], eluent: 0.5% NH_4OH in [5% MeOH in $CHCl_3$]) to afford tetracycle **125** (23 mg, 84%). **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.20 (br. s., 1H), 3.73 (d, *J* = 16.8 Hz, 1H), 3.32–3.23 (m, 1H), 3.20–3.13 (m, 2H), 3.09 (td, *J* = 5.4, 12.6 Hz, 1H), 2.75–2.66 (m, 1H), 2.58 (d, *J* = 14.9 Hz, 1H), 2.46 (d, *J* = 15.1 Hz, 1H), 2.13–2.04 (m, 2H), 1.96 (dd, *J* = 6.1, 14.2 Hz, 1H), 1.68–1.60 (m, 1H), 1.50 (s, 9H), 1.57–1.46 (m, 2H), 1.37 (d, *J* = 13.7 Hz, 1H), 1.34–1.18 (m, 3H), 1.16–1.03 (m, 6H), 0.75 (d, *J* = 6.3 Hz, 3H), 0.39 (dt, *J* = 5.9, 13.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 171.5, 156.3, 79.0, 76.5, 56.0, 51.2, 50.6, 49.1, 44.3, 44.2, 42.9, 42.6, 40.1, 31.9, 29.9, 28.9, 27.8, 25.4, 22.3, 21.0, 16.8. **FTIR** (thin film) cm^{-1}: 3337, 2927, 1707, 1648, 1523, 1454, 1364, 1250, 1165, 1101, 735. **HRMS** (ESI) (*m/z*) calc'd for $C_{23}H_{39}N_2O_3$ $[M+H]^+$: 391.2955, found 391.2961. **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.48 (ninhydrin).

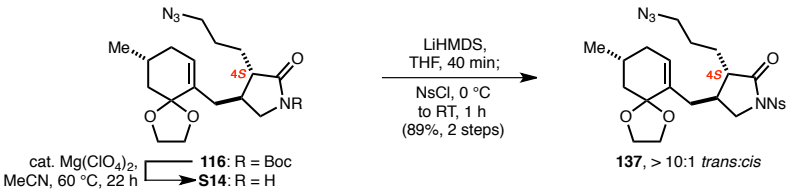


Valerolactam 132: 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (195 µL, 0.780 mmol, 1.30 equiv) was added dropwise via syringe to a stirred solution of **116** (300 mg, 0.600 mmol, 1.00 equiv) and cesium carbonate (391 mg, 1.20 mmol, 2.00 equiv) in DMF (1.5 mL). After 8 h, THF (6 mL) and a solution of TBAF in THF (1.0 M, 2.0 mL, 2.0 mmol, 3.3 equiv) was added dropwise via syringe to the stirred reaction mixture, which was subsequently warmed to 60 °C. After an additional 24 h, the stirred reaction mixture was allowed to cool to ambient temperature before 5% (w/v) sodium chloride solution (8 mL) and Et_2O (20 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with 5% (w/v) sodium chloride solution (4 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel treated with 1% Et_3N in EtOAc, eluent: gradient, 1% Et_3N in [2% MeOH in EtOAc] → 1% Et_3N in [8% MeOH in EtOAc]) to afford valerolactam **132** (216 mg, 88%) as a white foam. **^{1}H NMR** (600 MHz, $CDCl_3$, 3:2 mixture of C4-epimers; major epimer noted by *) δ: 5.80 (d, *J* = 4.1 Hz, 1H*), 5.77 (d, *J* = 4.4 Hz, 1H), 5.73 (br. s., 1H*; 1H), 5.07–4.98 (m, 1H*; 1H), 4.14–3.87 (m, 4H*; 4H), 3.31–3.21 (m, 2H*; 2H), 3.21–3.12 (m, 1H*; 1H), 3.11–3.04 (m, 1H*; 1H), 2.80–2.72 (m, 1H), 2.61–2.53 (m, 1H*), 2.48–2.41 (m, 1H*), 2.40–2.34 (m, 1H), 2.21 (d, *J* = 13.8 Hz, 1H*), 2.15–2.07 (m, 1H*; 2H), 2.06–1.97 (m, 1H*), 1.96–1.53 (m, 7H*; 8H), 1.41 (s, 9H*; 9H), 1.35–1.27 (m, 1H*; 1H), 0.94 (d, *J* = 6.4 Hz, 3H; 3H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 174.5, 173.9, 156.1, 155.9, 135.1, 135.0, 131.7, 130.4, 108.4, 108.3, 78.5, 65.4, 64.1, 64.0, 60.3, 43.2, 42.8, 42.6, 42.4, 42.3, 42.0, 41.9, 38.7, 37.1, 34.2, 34.0, 30.3, 30.1, 28.42, 28.38, 27.5, 27.4, 22.6, 22.4, 21.7, 21.4, 21.0, 19.1, 14.1, 13.6. **FTIR** (thin film) cm^{-1}: 3316, 2929, 1707, 1655, 1491, 1364, 1248, 1171,

1122, 1090, 1045, 966, 679. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{36}N_2NaO_5$ $[M+Na]^+$: 431.2516, found 431.2502. **TLC** (5% MeOH in CH_2Cl_2), R_f: 0.25 (anis).



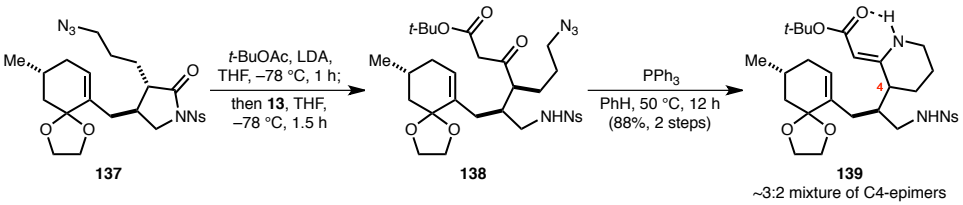
***N*-Boc-protected Valerolactam 135:** Di-*tert*-butyl dicarbonate (44 mg, 0.20 mmol, 1.5 equiv) was added in one portion to a stirred solution of valerolactam **132** (54 mg, 0.13 mmol, 1.0 equiv), 4-dimethylaminopyridine (17.7 mg, 0.145 mmol, 1.10 equiv), and Et_3N (56 µL, 0.40 mmol, 3.0 equiv) in CH_2Cl_2 (660 µL). After 24 h, additional di-*tert*-butyl dicarbonate (44 mg, 0.20 mmol, 1.5 equiv) and 4-dimethylaminopyridine (17.7 mg, 0.145 mmol, 1.10 equiv) were added to the stirred reaction mixture. After 14 h, additional di-*tert*-butyl dicarbonate (44 mg, 0.20 mmol, 1.5 equiv) and Et_3N (56 µL, 0.40 mmol, 3.0 equiv) were added to the stirred reaction mixture. After an additional 12 h, the reaction mixture was concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 1% Et_3N in hexanes, eluent: gradient, 1% Et_3N in [10% EtOAc in hexanes] → 1% Et_3N in [17% EtOAc in hexanes]) to afford *N*-Boc-protected valerolactam **135** (50 mg, 75%). **^{1}H NMR** (600 MHz, $CDCl_3$, 2:1 mixture of C4-epimers; major epimer noted by *) δ: 5.82 (d, *J* = 4.7 Hz, 1H*), 5.76 (d, *J* = 3.8 Hz, 1H), 5.00–4.94 (m, 1H*), 4.86–4.80 (m, 1H), 4.14–3.87 (m, 4H*; 4H), 3.73–3.65 (m, 1H*; 1H), 3.56–3.45 (m, 1H*; 1H), 3.22–3.04 (m, 2H*; 2H), 2.83–2.77 (m, 1H), 2.59–2.44 (m, 2H*; 1H), 2.22 (d, *J* = 13.8 Hz, 1H*), 2.15–2.07 (m, 1H*; 2H), 2.05–1.99 (m, 1H*), 1.96–1.55 (m, 7H*; 8H), 1.52 (s, 9H), 1.51 (s, 9H*), 1.41 (s, 9H*), 1.40 (s, 9H), 1.35–1.27 (m, 1H*; 1H), 0.94 (d, *J* = 6.7 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 174.0, 173.5, 156.2, 156.0, 152.7, 135.1, 131.8, 130.6, 108.3, 82.7, 82.6, 78.7, 65.5, 65.4, 64.2, 64.1, 46.4, 46.3, 46.0, 45.4, 42.4, 42.3, 42.1, 41.9, 39.5, 37.4, 36.6, 34.2, 34.1, 30.5, 30.2, 29.7, 28.4, 28.0, 27.6, 27.5, 22.5, 22.4, 22.0, 21.5, 20.9. **FTIR** (thin film) cm^{-1}: 3370, 2929, 1763, 1707, 1514, 1366, 1249, 1146, 852, 734. **HRMS** (ESI) (*m/z*) calc'd for $C_{27}H_{44}N_2NaO_7$ $[M+Na]^+$: 531.3041, found 531.3022. **TLC** (50% EtOAc in hexanes), R_f: 0.69 (anis).



***N*-2-Nitrobenzenesulfonyl-2-pyrrolidinone 137:** Magnesium perchlorate (48 mg, 0.22 mmol, 0.20 equiv) was added in a single portion to a stirred solution of **116** (467 mg, 1.08 mmol, 1.00 equiv) in MeCN (10 mL), and the resultant stirred reaction mixture was heated to 60 °C. After 22 h, the reaction mixture was allowed to cool to ambient temperature before Et_2O (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude 2-pyrrolidinone **S14** (342 mg) as a light pink solid, which was used without further purification.

A round-bottom flask was charged with crude **S14** (342 mg, 1.02 mmol, 1.00 equiv), azeotropically dried with three portions of benzene, and then charged with THF (6.8 mL). A solution of freshly prepared lithium bis(trimethylsilyl)amide in THF/hexanes (1.00 M, 1.23 mL, 1.23 mmol, 1.20 equiv) was added dropwise via syringe to the stirred reaction mixture. After 40 min, the reaction mixture was cooled to 0 °C and 2-nitrobenzenesulfonylchloride (295 mg, 1.33 mmol, 1.30 equiv) was added in a single portion. After 5 min, the reaction mixture was allowed to warm to ambient temperature. After 1 h, saturated aqueous NH_4Cl (5 mL) and Et_2O (8 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel treated with 1% Et_3N in [20% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [20% EtOAc in hexanes] → 1% Et_3N in [25% EtOAc in hexanes] → 1% Et_3N in [33% EtOAc in hexanes]) to afford *N*-Ns-2-pyrrolidinone **137** (498 mg, 89%) as a pale-yellow flocculent solid (>10:1 mixture of epimers at C4). **^{1}H NMR** (500 MHz, $CDCl_3$, >10:1 mixture of C4-epimers;

major (4*S*)-epimer reported) δ: 8.47–8.41 (m, 1H), 7.81–7.71 (m, 3H), 5.81 (d, *J* = 3.4 Hz, 1H), 4.16–4.06 (m, 2H), 4.06–3.99 (m, 1H), 3.99–3.90 (m, 2H), 3.54 (dd, *J* = 7.9, 10.1 Hz, 1H), 3.23 (t, *J* = 6.6 Hz, 2H), 2.54–2.42 (m, 2H), 2.25 (td, *J* = 6.0, 9.2 Hz, 1H), 2.17 (td, *J* = 4.7, 17.7 Hz, 1H), 2.07 (dd, *J* = 9.5, 14.2 Hz, 1H), 1.97–1.87 (m, 1H), 1.86 (dd, *J* = 1.5, 13.2 Hz, 1H), 1.80–1.71 (m, 1H), 1.71–1.60 (m, 3H), 1.59–1.49 (m, 1H), 1.30 (t, *J* = 12.9 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 175.3, 148.0, 134.9, 134.4, 133.8, 132.1, 132.0, 131.6, 124.2, 108.0, 65.3, 64.0, 51.2, 51.0, 48.4, 41.6, 37.2, 34.1, 34.0, 27.4, 26.0, 25.8, 21.4. **FTIR** (thin film) cm^{-1}: 2951, 2097, 1734, 1543, 1366, 1173, 1126, 592. **HRMS** (ESI) (*m/z*) calc'd for $C_{23}H_{29}N_5NaO_7S$ $[M+Na]^+$: 542.1680, found 542.1680. **TLC** (33% EtOAc in hexanes), R_f: 0.28 (UV, anis).

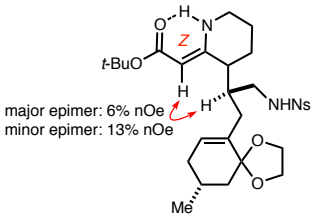


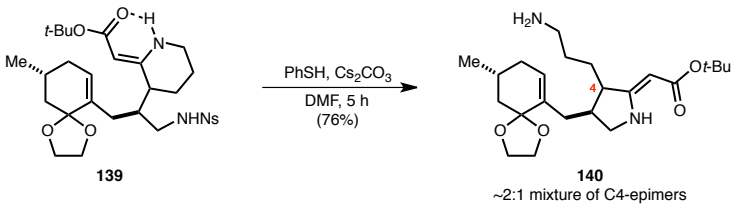
Vinylogous urethane (*Z*)-14: A solution of *n*-butyllithium in hexanes (2.54 M, 1.13 mL, 2.88 mmol, 3.00 equiv) was added dropwise via syringe to a stirred solution of diisopropylamine (0.443 mL, 3.16 mmol, 3.30 equiv) in THF (5.6 mL) at –78 °C. After 10 min, the stirred reaction mixture was allowed to warm to 0 °C, and after 30 min it was re-cooled to –78 °C. *t*-Butylacetate (0.389 mL, 2.88 mmol, 3.00 equiv) was then added dropwise via syringe to the stirred reaction mixture at –78 °C. After 1 h, a cooled solution of **137** (498 mg, 0.958 mmol, 1.00 equiv), which was azeotropically dried with three portions of benzene, in THF (2 mL) at –78 °C was added dropwise via a dry-ice wrapped cannula to the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 5 mL). After 85 min, saturated aqueous NH_4Cl solution (10 mL) was added to the red reaction mixture at –78 °C, and the resultant suspension was allowed to warm to ambient temperature. Et_2O (10 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude β-ketoester **138** (590 mg) as a pale-yellow flocculent solid, which was used without further purification.

Triphenylphosphine (365 mg, 1.39 mmol, 1.50 equiv) was added in a single portion to a stirred solution of crude **138** (590 mg, 0.928 mmol, 1.00 equiv) in benzene (9.3 mL), and the resultant stirred reaction mixture was subsequently heated to 50 °C. After 12 h, the stirred reaction mixture was allowed to cool to ambient temperature before being concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 1% Et_3N in [20% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [20% EtOAc in hexanes] → 1% Et_3N in [33% EtOAc in hexanes] → 1% Et_3N in [50% EtOAc in hexanes]) to afford vinylogous urethane (*Z*)-**139** (500 mg, 88%) as a pale-yellow flocculent solid (~3:2 mixture of epimers at C4). **^{1}H NMR** (500

MHz, C_6D_6, 3:2 mixture of C4-epimers; major epimer noted by *) δ: 9.27 (br. s., 1H), 9.23 (br. s., 1 H*), 7.97 (dd, *J* = 1.3, 7.9 Hz, 1 H*), 7.92 (dd, *J* = 1.2, 7.8 Hz, 1H), 6.95 (dd, *J* = 1.2, 8.1 Hz, 1 H*), 6.97 (dd, *J* = 1.0, 8.1 Hz, 1H), 6.78 (dt, *J* = 1.2, 7.7 Hz, 1 H*), 6.74 (dt, *J* = 1.2, 7.7 Hz, 1H), 6.58 (dt, *J* = 1.3, 7.8 Hz, 1 H*), 6.53 (dt, *J* = 1.5, 7.8 Hz, 1H), 6.01 (t, *J* = 5.7 Hz, 1H), 5.90 (t, *J* = 6.2 Hz, 1 H*), 5.55 (d, *J* = 4.2 Hz, 1 H*), 5.45 (d, *J* = 3.4 Hz, 1H), 4.86 (s, 1H), 4.54 (s, 1 H*), 3.97–3.89 (m, 1 H*), 3.81–3.71 (m, 1 H; 2 H*), 3.68–3.58 (m, 2H), 3.56–3.48 (m, 1 H*), 3.48–3.41 (m, 1H), 3.30 (td, *J* = 5.5, 13.2 Hz, 1 H*), 3.14 (td, *J* = 4.2, 12.8 Hz, 1H), 3.03–2.92 (m, 1 H; 1 H*), 2.66–2.58 (m, 2H), 2.58–2.47 (m, 2 H*), 2.47–2.36 (m, 2 H*), 2.37–2.28 (m, 2H), 2.27–2.19 (m, 1 H*), 2.17–2.12 (m, 2H), 2.00–1.80 (m, 2 H; 2 H*), 1.77 (d, *J* = 12.9 Hz, 1 H*), 1.71 (d, *J* = 12.9 Hz, 1H), 1.61 (dd, *J* = 11.7, 13.7 Hz, 1 H*), 1.55 (s, 9H), 1.53 (s, 9 H*), 1.47–1.33 (m, 3 H; 2 H*), 1.33–1.16 (m, 2 H; 2 H*), 1.15–0.95 (m, 1 H; 2 H*), 0.80 (d, *J* = 6.6 Hz, 3 H)*, 0.78 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 171.8, 171.7, 164.8, 164.6, 148.8, 135.9, 135.3, 135.0, 134.6, 133.1, 132.9, 132.3, 132.2, 131.7, 131.4, 125.2, 125.2, 108.9, 108.8, 83.7, 82.9, 78.0, 77.6, 65.7, 65.4, 64.5, 64.1, 45.6, 44.6, 42.5, 42.4, 41.3, 41.2, 41.1, 40.5, 40.1, 39.7, 34.8, 34.6, 31.5, 30.4, 29.3, 28.0, 21.9, 21.9, 21.7, 21.3. **FTIR** (thin film) cm^{-1}: 3273, 2951, 1638, 1597, 1541, 1364, 1148, 588. **HRMS** (ESI) (*m/z*) calc'd for $C_{29}H_{41}N_3NaO_8S$ $[M+Na]^+$: 614.2507, found 614.2502. **TLC** (33% EtOAc in hexanes), R_f: 0.23 (UV, anis).

1D NOESY (500 MHz, C_6D_6):



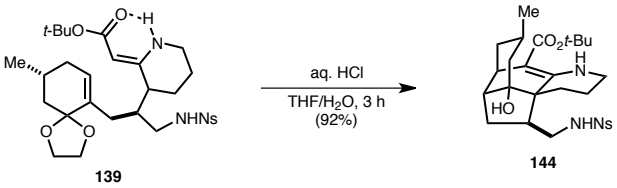


139 **140**
~2:1 mixture of C4-epimers

5-membered vinylogous urethane 140: Thiophenol (26 µL, 0.25 mmol, 3.0 equiv) was added dropwise via syringe to a stirred solution of **139** (48 mg, 0.085 mmol, 1.00 equiv) and cesium carbonate (420 µL) at 0 °C, which was subsequently allowed to warm to ambient temperature after 5 min. After 5 h, water (5 mL) and EtOAc (5 mL) were added to the stirred reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel treated with 0.2% NH_4OH in [1.8% MeOH in $CHCl_3$], eluent: 1% NH_4OH in [9% MeOH in $CHCl_3$]) to afford 5-membered vinylogous urethane **140**[68] (25 mg, 76%) as a yellow flocculent solid (~2:1 mixture of C4-epimers). **^{1}H NMR** (500 MHz, $CDCl_3$, ~2:1 mixture of C4-epimers; major epimer noted by *) δ: 7.81–7.69 (m, 1H*; 1H), 5.70–5.65 (m, 1H*; 1H), 4.40 (s, 1H*; 1H), 4.09–3.88 (m, 4H*; 4H), 3.57 (dd, *J* = 7.0, 10.1 Hz, 2H*), 3.37 (dd, *J* = 6.3, 9.8 Hz, 1H), 3.24 (ddd, *J* = 0.7, 4.6, 10.0 Hz, 1H), 3.10 (ddd, *J* = 1.0, 4.3, 10.1 Hz, 1H*), 2.73–2.66 (m, 2H*; 2H), 2.62 (q, *J* = 6.8 Hz, 1H), 2.57–2.49 (m, 1H), 2.40–2.34 (m, 1H*), 2.32–2.24 (m, 1H*), 2.21 (dd, *J* = 5.5, 15.0 Hz, 1H*; 1H), 2.16–2.07 (m, 1H*; 1H), 1.98 (dd, *J* = 9.6, 14.3 Hz, 1H*), 1.93–1.71 (m, 5H*; 6H), 1.69–1.43 (m, 13H*; 13H), 1.35–1.23 (m, 1H*; 1H), 0.95 (d, *J* = 6.6 Hz, 3H*; 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 171.2, 170.9, 168.9, 168.3, 135.3, 135.2, 130.6, 130.5, 108.2, 108.2, 78.3, 78.1, 77.8, 65.4, 65.3, 64.1, 63.9, 51.0, 49.7, 49.4, 46.6, 42.2, 42.0, 41.8, 39.5, 38.0, 34.4, 34.1, 34.0, 31.4, 30.6, 29.7, 28.7, 27.5, 27.4, 27.0, 23.7, 21.5. **FTIR** (thin film) cm^{-1}: 2441, 2978, 2933, 1691, 1390,

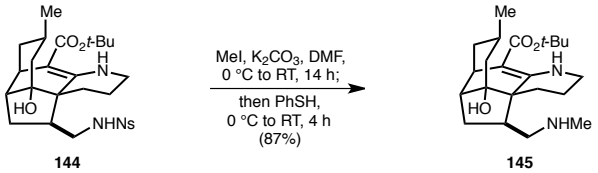
[68] NOESY1D experiments revealed coupling between C6–H and presumably the C4/C3–H atoms, but due to the overlapping peaks in the spectrum, the stereochemistry of the vinylogous urethane could not be unambiguously assigned.

1377, 1256, 1172, 1093, 847. **HRMS** (ESI) (*m/z*) calc'd for $C_{23}H_{39}N_2O_4$ $[M+H]^+$: 407.2904, found 407.2902. **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.58 (UV, anis).



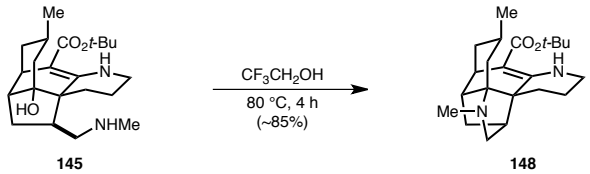
139 144

Tetracyclic 2-nitrobenzenesulfonamide (–)-144: Aqueous HCl (1.2 M, 20 mL) was added to a stirred solution of **139** (500 mg, 0.845 mmol, 1.00 equiv) in THF (156 mL). After 4.5 h, Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel treated with 1% Et_3N in [25% EtOAc in hexanes], eluent: gradient, 1% Et_3N in [25% EtOAc in hexanes] → 1% Et_3N in [33% EtOAc in hexanes] → 1% Et_3N in [40% EtOAc in hexanes] → 1% Et_3N in [50% EtOAc in hexanes]) to afford tetracyclic 2-nitrobenzenesulfonamide (–)-**144** (425 mg, 92%) as an orange flocculent solid. **^{1}H NMR** (500 MHz, C_6D_6) δ: 9.41 (br. s., 1H), 7.90 (dd, *J* = 1.0, 7.9 Hz, 1H), 6.96 (dd, *J* = 0.9, 8.0 Hz, 1H), 6.74 (dt, *J* = 1.1, 7.8 Hz, 1H), 6.57 (dt, *J* = 1.4, 7.8 Hz, 1H), 6.29 (t, *J* = 4.8 Hz, 1H), 3.26–3.11 (m, 2H), 2.89 (d, *J* = 2.1 Hz, 1H), 2.70–2.64 (m, 1H), 2.54 (dt, *J* = 4.1, 12.0 Hz, 1H), 2.04 (qd, *J* = 4.6, 11.8 Hz, 1H), 1.89 (td, *J* = 3.5, 11.3 Hz, 1H), 1.75–1.62 (m, 3H), 1.57–1.51 (m, 2H), 1.50 (s, 9H), 1.43 (dd, *J* = 9.5, 12.9 Hz, 1H), 1.36–1.21 (m, 1H), 1.14–1.06 (m, 2H), 0.86 (dt, *J* = 1.8, 12 Hz, 1H), 0.80 (d, *J* = 6.4 Hz, 3H), 0.77 (br. s, 1H), 0.58 (dd, *J* = 12.1, 13.3 Hz, 1H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 170.6, 164.6, 148.8, 135.0, 132.9, 132.1, 131.2, 125.0, 88.7, 80.5, 78.1, 51.4, 49.3, 49.0, 46.2, 43.1, 41.2, 40.8, 40.2, 31.5, 29.1, 26.8, 22.7, 20.8, 20.6. **FTIR** (thin film) cm^{-1}: 3273, 3374, 3252, 2926, 1634, 1591, 1541, 1362, 1263, 1161, 1144, 731. **HRMS** (ESI) (*m/z*) calc'd for $C_{27}H_{37}NaN_3O_7S$ $[M+Na]^+$: 570.2244, found 570.2241. **$[\alpha]_D^{25}$**: –86 (*c* = 1.0, $CHCl_3$). **TLC** (33% EtOAc in hexanes), R_f: 0.23 (UV, $KMnO_4$).



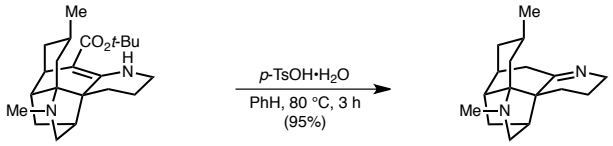
144 145

Tetracyclic *N*-methylamine 145: Iodomethane (71 μL, 1.13 mmol, 2.00 equiv) was added dropwise via syringe to a vigorously stirred solution of anhydrous potassium carbonate (391 mg, 2.83 mmol, 5.00 equiv) and (–)-**144** (310 mg, 0.566 mmol, 1.00 equiv) in DMF (3.8 mL) at 0 °C, and the resultant reaction mixture was allowed to warm to ambient temperature. After 14 h, the reaction mixture was cooled to 0 °C before thiophenol (291 μL, 2.83 mmol, 5.00 equiv) was added dropwise via syringe, and the resultant vigorously stirred mixture was allowed to warm to ambient temperature. After 4 h, water (4 mL) was added to the stirred reaction mixture, which was then extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with water (3 × 15 mL) and brine (1 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel treated with 0.5% NH_4OH in [5% MeOH in $CHCl_3$], eluent: gradient, 0.5% NH_4OH in [5% MeOH in $CHCl_3$] → 1% NH_4OH in [9% MeOH in $CHCl_3$] → 2% NH_4OH in [18% MeOH in $CHCl_3$]) to afford **145** (186 mg, 87%) as a white flocculent solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.12 (br. s, 1H), 3.31–3.25 (m, 1H), 3.19–3.12 (td, *J* = 11.7, 4.2 Hz, 1H), 2.79–2.76 (m, 1H), 2.73 (dd, *J* = 4.4, 14.2 Hz, 1H), 2.51 (dd, *J* = 2.4, 14.2 Hz, 1H), 2.42 (s, 3H), 2.42–2.37 (m, 1H), 1.94–1.87 (m, 2H), 1.85–1.79 (m, 1H), 1.79–1.57 (m, 7H), 1.43 (s, 9H), 1.14 (dd, *J* = 12.2, 14.2 Hz, 1H), 0.93 (dt, *J* = 2.2, 12.5 Hz, 1H), 0.85 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.6, 165.9, 88.4, 77.7, 77.7, 52.1, 50.3, 49.9, 49.4, 41.1, 40.8, 40.6, 39.6, 36.8, 29.2, 28.7, 25.8, 22.4, 20.9, 20.6. **FTIR** (thin film) cm^{-1}: 3248, 3148, 2924, 1630, 1589, 1261, 1248, 1163, 1140, 733. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{37}N_2O_3$ $[M+H]^+$: 377.2799, found 377.2826. **TLC** (2% NH_4OH in [18% MeOH in $CHCl_3$]), R_f: 0.20 (ninhydrin).

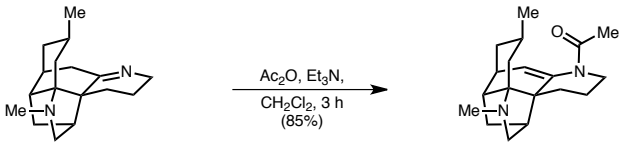


145 148

Pentacycle (–)-148: A Schlenk flask was charged with **145** (163 mg, 0.430 mmol, 1.00 equiv) and 2,2,2-trifluoroethanol (8.6 mL), and the resultant solution was degassed via FPT (four iterations). The Schlenk flask was then sealed under an argon atmosphere, and heated to 80 °C. After 4 h, the stirred reaction mixture was cooled to ambient temperature, transferred to a round-bottom flask, and concentrated under reduced pressure to afford crude pentacyclic vinylogous urethane (–)-**148** (136 mg) as a slightly pink solid, which contained ~12% TFE by ^{1}H NMR but was otherwise pure. This corresponds to approximately 131 mg of pure **148** and an ~85% yield. Crude **148** was carried onto the next reaction without further purification, but an analytical sample could be prepared by azeotropically distilling **148** with three portions of benzene and three portions of $CDCl_3$. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.05 (br. s, 1H), 3.34–3.22 (m, 2H), 2.71 (dd, *J* = 3.7, 6.9 Hz, 1H), 2.32 (s, 3H), 2.25 (m, 1H), 2.19–2.12 (m, 2H), 2.02 (d, *J* = 13.5 Hz, 1H), 1.87–1.71 (m, 3H), 1.68 (dd, *J* = 1.6, 13.0 Hz, 1H), 1.59–1.53 (m, 2H), 1.52–1.45 (m, 1H), 1.44 (s, 9H), 1.29 (dd, *J* = 8.0, 12.6 Hz, 1H), 1.14 (t, *J* = 13.0 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.83–0.77 (dt, *J* = 2.3, 12.5 Hz, 1H), 0.06 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.4, 162.4, 90.3, 77.8, 66.3, 59.9, 52.2, 44.4, 41.6, 39.1, 38.7, 38.3, 35.1, 34.7, 33.6, 28.7, 24.7, 22.5, 20.6, 20.5. **FTIR** (thin film) cm^{-1}: 3248, 3163, 2926, 1636, 1597, 1454, 1234, 1168, 1148, 1123. **HRMS** (ESI) (*m/z*) calc'd for $C_{22}H_{35}N_2O_2$ $[M+H]^+$: 359.2693, found 359.2718. **$[\alpha]_D^{25}$**: –90 (*c* = 1.0, $CHCl_3$). **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.49 (ninhydrin).



Pentacyclic imine S15: A round-bottom flask equipped with a cold-finger was charged with crude **148** (38 mg, 0.11 mmol, 1.0 equiv) and benzene (11 mL). *p*-Toluenesulfonic acid monohydrate (61 mg, 0.32 mmol, 3.0 equiv) was added as a single portion to the stirred solution, and the resultant stirred reaction mixture was subsequently heated to 80 °C. After 3 h, the reaction was allowed to cool to ambient temperature and concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 1% NH_4OH in [9% MeOH in $CHCl_3$], eluent: 1% NH_4OH in [9% MeOH in $CHCl_3$]) to afford **S15** (26 mg, 95%) as a yellow oil that was carried forward immediately. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.66 (br. d, *J* = 17.8 Hz, 1H), 3.61–3.51 (m, 1H), 3.38 (td, *J* = 3.1, 9.0 Hz, 1H), 2.73 (dddd, *J* = 3.4, 7.8, 15.4, 18.3 Hz, 1H), 2.34 (s, 3H), 2.28 (t, *J* = 6.6 Hz, 1H), 2.20 (d, *J* = 18.3 Hz, 1H), 2.12–2.08 (m, 1H), 2.09 (d, *J* = 9.3 Hz, 1H), 2.05 (t, *J* = 3.9 Hz, 1H), 1.90–1.83 (m, 1H), 1.79–1.49 (m, 7H), 1.41 (dd, *J* = 8.3, 13.4 Hz, 1H), 1.16 (t, *J* = 12.8 Hz, 1H), 1.04 (dt, *J* = 2.7, 12.5 Hz, 1H), 0.88 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 174.4, 68.7, 61.6, 54.4, 50.0, 44.2, 41.4, 39.2, 38.8, 35.3, 34.6, 33.7, 32.1, 25.5, 23.0, 21.9, 21.6. **FTIR** (thin film) cm^{-1}: 2916, 1636, 1454, 1150. **HRMS** (ESI) (*m/z*) calc'd for $C_{17}H_{27}N_2$ $[M+H]^+$: 259.2169, found 259.2157. **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.36 (ninhydrin).



S15 (+)-fastigiatine (**37**)

(+)-**Fastigiatine (37):** Acetic anhydride (95 μL, 1.0 mmol, 10 equiv) was added dropwise via syringe to a stirred solution of **S15** (26.1 mg, 0.101 mmol, 1.00 equiv) and Et_3N (140 μL, 1.0 mmol, 10 equiv) in CH_2Cl_2 (1 mL). After 3 h, the stirred reaction mixture was concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel treated with 0.5% NH_4OH in [5% MeOH in $CHCl_3$], eluent: 0.5% NH_4OH in [5% MeOH in $CHCl_3$]) to afford (+)-fastigiatine (**37**) (25.7 mg, 85%) as a colorless solid. Crystals suitable for X-ray diffraction were obtained by slow evaporation of a solution of (+)-**37** in Et_2O at ambient temperature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 5.19 (d, *J* = 5.4 Hz, 1H), 3.82 (dt, *J* = 5.9, 11.8 Hz, 1H), 3.29–3.22 (m, 2H), 2.42–2.38 (m, 1H), 2.33 (s, 3H), 2.20 (d, *J* = 9.3 Hz, 1H), 2.18–2.15 (m, 1H), 2.15 (s, 3H), 2.08 (br. d, *J* = 15.1 Hz, 1H), 2.05–1.95 (m, 1H), 1.94–1.90 (m, 1H), 1.79–1.72 (m, 1H), 1.70 (dd, *J* = 4.8, 14.3 Hz, 1H), 1.61–1.54 (m, 3H), 1.45–1.32 (m, 2H), 1.20 (t, *J* = 12.9 Hz, 1H), 1.02 (dt, *J* = 2.6, 12.6 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.2, 139.3, 123.3, 65.6, 59.8, 55.2, 45.6, 45.5, 40.3, 38.5, 37.5, 35.2, 34.7, 34.0, 25.7, 23.1, 22.5, 21.7, 21.3. **FTIR** (thin film) cm^{-1}: 2943, 1651, 1454, 1383. **HRMS** (ESI) (*m/z*) calc'd for $C_{19}H_{28}NaN_2O$ $[M+Na]^+$: 323.2094, found 323.2095. **$[\alpha]_D^{24}$**: +375 (*c* = 1.4, $CHCl_3$). **TLC** (9% MeOH and 1% NH_4OH in $CHCl_3$), R_f: 0.44 (ninhydrin).

II. Total Syntheses of HMP-Y1, Hibarimicinone, and HMP-P1

Chapter 3

Introduction to the Hibarimicin Natural Products

Introduction

In 1993, a new class of natural products, the angelmicins, was identified from the rare actinomycete *Microbispora* subsp. AA9966 by a team of Japanese scientists during a screen for novel microbial inhibitors of cellular oncogenic transformation.[69] They found that angelmicins A and B (**1** and **2**, respectively, Figure 3.1) inhibited the growth of Src and Abl transformed NIH3T3 cells with IC_{50} values between 1-5 μg/mL and inhibited Src kinase activity. In 1996, a more comprehensive biological study revealed that angelmicins A–D dose-dependently inhibited the growth of several human cancer cell leukemia lines in a four-day growth assay.[70] In particular, angelmicin B (**2**) has the most potent anti-proliferative activity in HL-60 cells (IC_{50} = 58 nM) and induces their differentiation. Interestingly, the Japanese team also determined that the IC_{50} concentration of angelmicin B (**2**) needed for Src kinase inhibition was on the order of 100-fold higher than that for growth inhibition, suggesting that the cellular target responsible for the cytotoxic effects of **2** is not Src.

That same year, the two-dimensional structure of angelmicin B (**2**) was elucidated by ^{1}H, ^{13}C, COSY, TOCSY, HMBC, and NOESY NMR experiments as well as by FABMS, IR, and UV–vis data.[71] The data revealed that **2** was an extraordinary complex type-II polyketide that was pseudo-C_2-symmetric about its highly hindered C2–C2' bond and contained six 2-deoxyglycosides. The C_2-symmetry of **2** is broken by oxidation of the B-, C-, and D-rings relative to the G-, F-, and E-rings, respectively. More specifically, the B-ring contains a cyclic ether bridging C8' and C13', the C-ring contains a hydroxyl group at C6', and the D-ring is a quinone. In 1998, a Hori and coworkers isolated hibarimicins A–G from the culture broth of the rare actinomycete *Microbispora rosea* subsp. *hibaria*

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[69] (a) Uehara, Y.; Li, P. M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiot*. **1993**, *46*, 1306–1308. (b) The angelmicins are structurally identical to the hibarimicins (vide infra).

[70] Yokoyama, A.; Okabe-Kado, J.; Uehara, Y.; Oki, T.; Tomoyasu, S.; Tsuruoka, N.; Honma, Y. *Leukemia Res*. **1996**, *20*, 491–497.

[71] Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett*. **1996**, *37*, 2785–2788.

TP-A0121.[72] It was soon determined that the hibarimicins are structurally identical to the angelmicins, and these natural products from hereon are referred to as the hibarimicins. Hibarimicins A–G structurally differ by variation of the 2-deoxy-glycosides that adorn a shared unprecedented highly-oxidized aglycon, hibarimicinone (**6**). The relative stereochemistry of the hibarimicins was determined by NOESY correlations. However, the relative stereochemistry between the "eastern" and "western" halves of **6** as well as between the carbohydrates and **6** could not be determined due to their relative isolation from one another. Nonetheless, the pseudo-C_2-symmetry of **6**, together with additional studies investigating the biosynthesis of the hibarimicins, strongly supported the

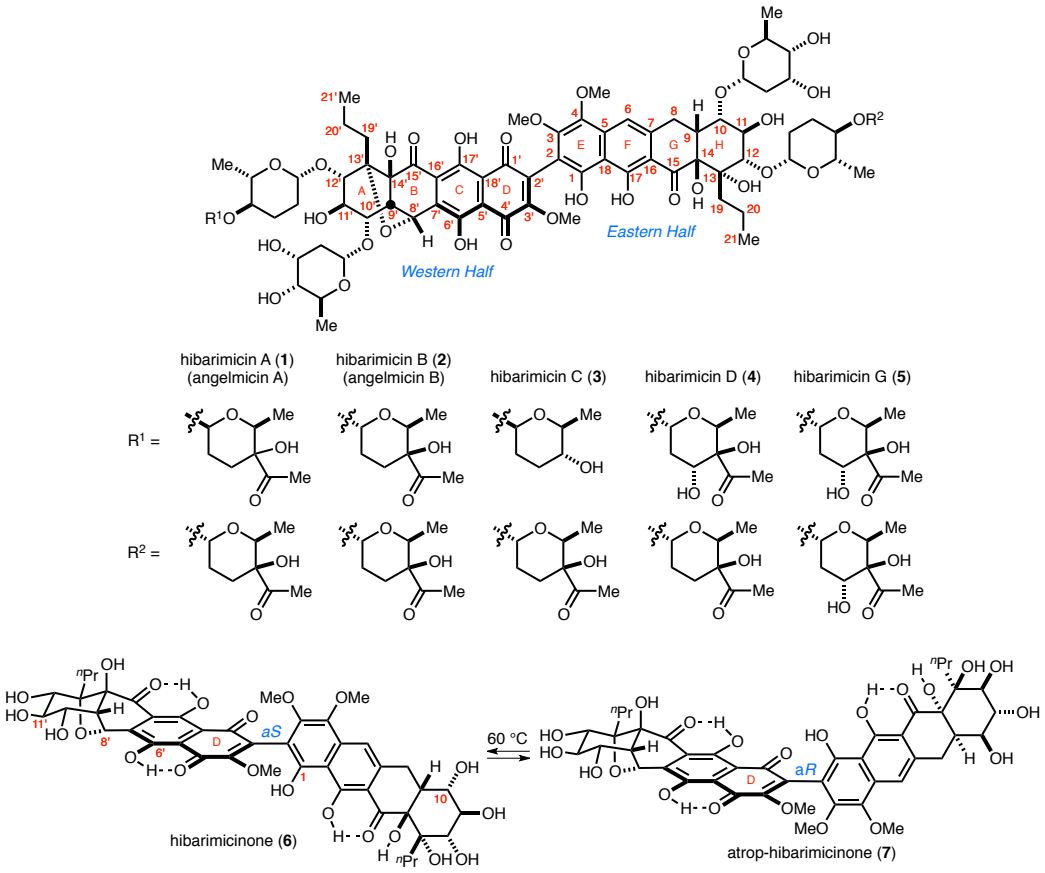

Figure 3.1 Structures of hibarimicins A–G (**1**-**5**) and hibarimicinone (**6**).

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[72] (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 394–401. (b) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 402–417.

hypothesis that each half possessed the same absolute stereochemistry (vide infra).[73]

In 2004, another study by Hori and coworkers tentatively assigned the absolute stereochemistry of the hibarimicins.[74a] The 2-deoxy-glycosides were cleaved from **2** and their absolute stereochemistry was confirmed by comparison to authentic samples. The absolute stereochemistry of hibarimicinone (**6**) was assigned by synthesis of a multi-MPTA ester derivative at the C1-, C10-, and C11'-hydroxyls, and comparison to a simple B/G-ring model system. Lastly, it was demonstrated that **6** exhibits axial chirality about its highly congested C2–C2' bond, and that **6** is isolated as a single atropisomer. The axial stereochemistry of **6** was assigned the a*S* configuration by the CD exciton chirality method. Interestingly, heating a solution of **6** in methanol to 60 °C led to rapid isomerization about the C2–C2' bond and ultimately a mixture of **6** and its atrop-diastereomer, atrop-hibarimicinone (**7**). Whether the glycosylated hibarimicins also easily isomerize about the C2–C2' bond has not yet been reported.

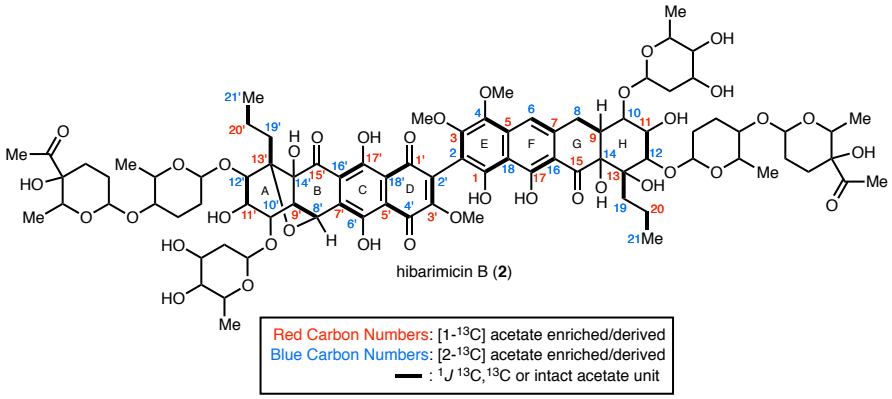

Figure 3.2 ^{13}C-Labeling studies on *Microbispora rosea* subsp. *hibaria* TP-A0121.

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[73] (a) Hori, H.; Kajiura, T.; Igarashi, Y.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 46–52. (b) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 53–60. (c) Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 61–70. (d) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.; Oki, T.; Uehara, Y. *J. Antibiot*. **2002**, *55*, 270–278.

[74] (a) Hori, H.; Igarashi, Y.; Kajiura, T.; Sato, S.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uehara, Y.; Oki, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2004**, *46*, 49–54. (b) Personal communication with Prof. H. Hori and Prof. Y. Igarashi.

The biosynthesis of the hibarimicins was investigated by ^{13}C-acetate labeling and blocked mutant studies with *Microbispora rosea* subsp. *hibaria* TP-A0121.[73] The ^{13}C-acetate labeling studies were conducted with sodium [1-^{13}C], [2-^{13}C], or [1,2-$^{13}C_2$] acetate and hibarimicin B (**2**) was isolated and probed by ^{13}C and 1D-INADEQUATE NMR experiments; the results are summarized in Figure 3.2. Enrichment of [2-^{13}C] at both C2 and C2' clearly suggested that **2** arises from a dimerization of two separate polyketide-derived monomers. This proposal is also directly supported by the blocked mutant studies. Mutagenesis of *Microbispora rosea* subsp. *hibaria* TP-A0121 led to the identification of novel metabolites, including HMP-Y1 (**8**) and HMP-P1 (**10**), as well as their glycosylated derivatives HMP-Y6 (**9**) and HMP-P4 (**11**) (Figure 3.3). After additional feeding studies with ^{13}C-acetate labeled C_2-symmetric **8**, it was discovered that **8** is a precursor to hibarimicinone (**6**), which is subsequently glycosylated to yield hibarimicins A–G. As one would expect, the C2–C2' chiral axis of **9** was assigned the a*R* stereochemistry by the CD exciton chirality method,[74b] which corresponds to the same relative stereochemistry as **6**.[75] The axial stereochemistry of **8** was not rigorously assigned since its CD-spectrum was not obtained; however, **8** is derived from glycolysis of **9** and—barring isomerization occurring during glycolysis—**8** should therefore also possess the a*R* configuration about C2–C2' as depicted in Figure 3.3.

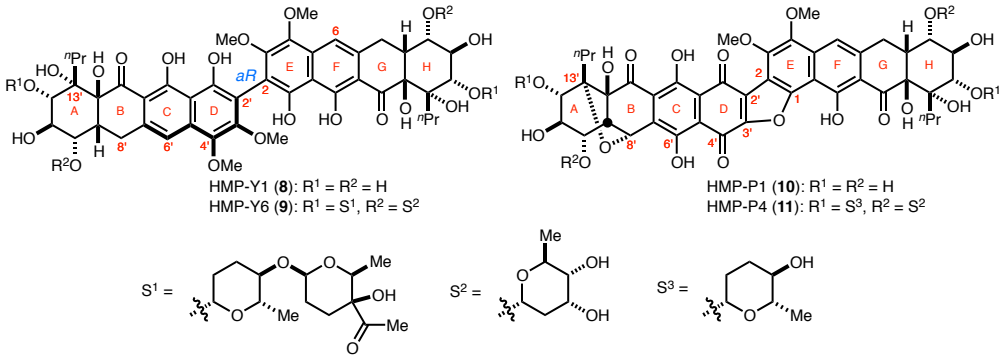

Figure 3.3 Metabolites from blocked mutants of *Microbispora rosea* subsp. *hibaria* TP-A0121.

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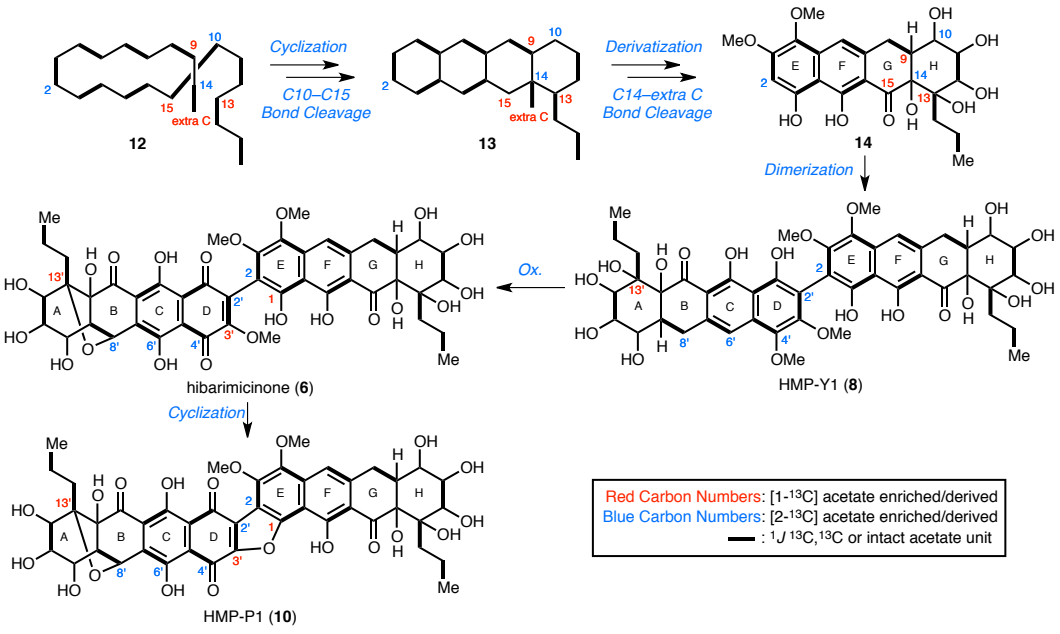
[75] Although **6** is assigned a*S* stereochemistry while **8** possesses a*R* stereochemistry, this is merely because of a switch in group priorities in accordance with Cahn–Ingold–Prelog sequence rules.

Based on their studies, Hori and coworkers proposed the biosynthesis shown in Scheme 3.1. 1D-INADEQUATE NMR experiments on [1,2-$^{13}C_2$] acetate labeled **2** led the authors to propose that each monomeric half of the aglycon was most likely derived from linear precursor **12**. The lack of one bond ^{13}C–^{13}C coupling between C14 and C15 as well as between C9 and C10 supports this model where C10 and C15 are originally linked and derived from the same original acetate unit in **12**. Linear precursor **12** then cyclizes and the C10–C15 bond is ultimately fragmented to give tetracyclic carbon skeleton **13**. Excision of the extra carbon unit, followed by functionalization, is then proposed to give monomer **14**, which is the eastern half of hibarimicinone (**6**) and half of HMP-Y1 (**8**). Dimerization of **14** then yields HMP-Y1 (**8**). A subsequent series of oxidations on the western half of **8** would then eventually afford hibarimicinone (**6**). Ostensibly, this conversion (**8** → **6**) proceeds by breaking the C_2-symmetry of **8** via oxidation of the B-, C-, and D-rings with concomitant demethylation of the C4'–OMe methyl group. Interestingly, HMP-Y6 (**9**) is not a precursor to hibarimicins A–G, and thus oxidation of **8** to **6** should precede glycosylation to give hibarimicins A–G. HMP-P1 (**10**) arises from **6** via cyclization of C1–OH onto C3' of the D-ring quinone and subsequent expulsion of methanol.



Scheme 3.1 Proposed biosynthesis of the hibarimicin natural products.

Selected Synthetic Efforts toward the Hibarimicin Natural Products

The hibarimicin natural products and the corresponding aglycons are challenging targets for organic synthesis. Despite efforts by various groups, these targets had resisted total synthesis[76] until 2012 when Tatsuta et al. reported the first synthesis[77] of hibarimicinone (**6**) and we later reported the synthesis of hibarimicinone (**6**) and the first total syntheses of atrop-hibarimicinone (**7**), HMP-Y1 (**8**),

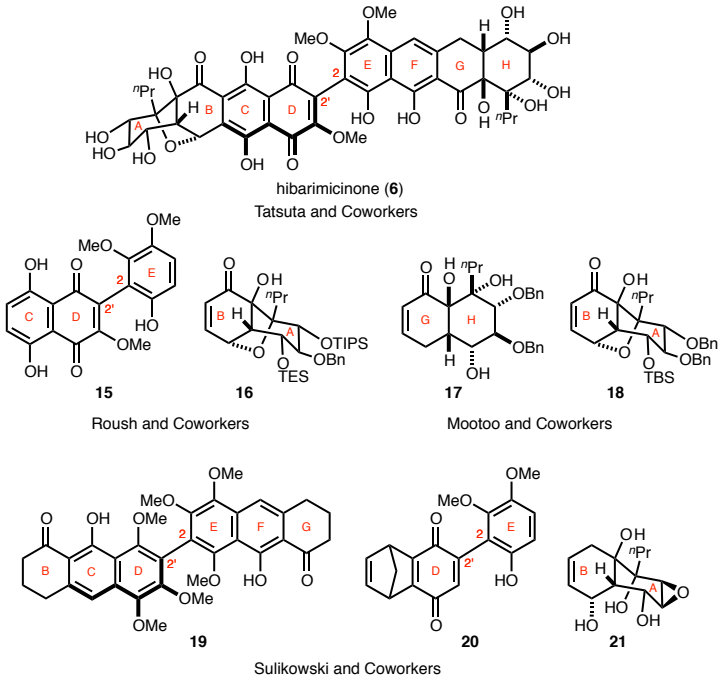


Figure 3.4 Summary of synthetic efforts toward the hibarimicins from other groups.

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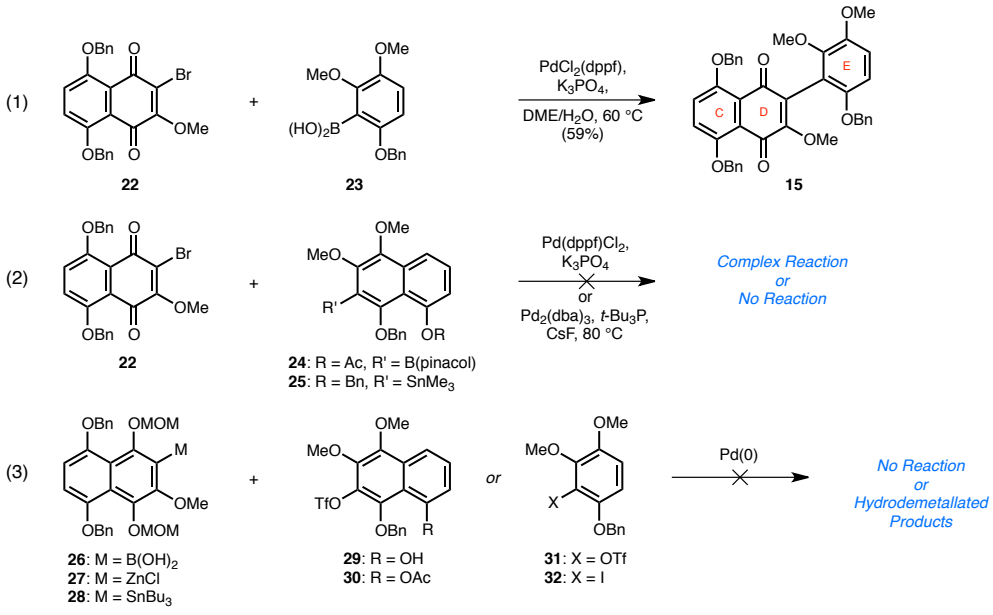
[76] For studies towards the hibarimicins or their related natural products, see: (a) Lee, C.-S.; Audelo, M. Q.; Reibenpies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403–4409. (b) Maharoof, U. S.; Sulikowski, G. A. *Tetrahedron Lett*. **2003**, *44*, 9021–9023. (c) Kim, K.; Mahroof, U. S.; Raushel, J.; Sulikowski, G. A. *Org*. *Lett*. **2003**, *5*, 2777–2780. (d) Narayan, S.; Roush, W. R. *Org*. *Lett*. **2004**, *6*, 3789–3792. (e) Lambert, W. T; Roush, W. R. *Org*. *Lett*. **2005**, *7*, 5501–5504. (f) Lee, W. D.; Kim, K.; Sulikowski, G. A. *Org*. *Lett*. **2005**, *7*, 1687–1689. (g) Li, J.; Todaro, L. J.; Mootoo, D. R. *Org*. *Lett*. **2008**, *10*, 1337–1340. (h) Li, J.; Todaro, L.; Mootoo, D. R. *Eur*. *J*. *Org*. *Chem*. **2011**, 6281–6287. (i) Romaine, I. M.; Hempel, J. E.; Shanmugam, G.; Hori H.; Igarashi, Y.; Polavarapu, P. L.; Sulikowski, G. A. *Org*. *Lett*. **2011**, *13*, 4538–4541.

[77] Tatsuta, K.; Fukuda, T.; Ishimori, T.; Yachi, R.; Yoshida, S.; Hashimoto, H.; Hosokawa, S. *Tetrahedron Lett*. **2012**, *53*, 422–425.

atrop-HMP-Y1, and HMP-P1 (**10**).[78] In this section, I will briefly cover selected prior synthetic efforts toward the hibarimicins—stressing strategies that constructed the central ring system with the C2–C2' bond—in order to provide sufficient context for the next chapter.

Roush and coworkers reported syntheses of CDE-ring system **15**[76d] and of AB-enone **16**[76e] (Figure 3.4). The CDE-ring system synthesis was accomplished via a Suzuki cross-coupling reaction between naphthazarin **22** and boronic acid **23** (Scheme 3.2, Eq. 1). The apparent straightforward nature of the depicted cross-coupling reaction belies the enormous effort spent attempting to form the C2–C2' bond; a representative sampling of their efforts is shown in Eq. 2 and 3 in Scheme 3.2. For example, very similar couplings, such as between **22** and naphthalenes **24** or **25**, were unsuccessful. Attempted cross-coupling of a variety of naphthyl organometallics (e.g., **26**-**28**) with various electrophiles (e.g., **29**-**32**) also proved fruitless (Scheme 3.2, Eq. 3). In addition to investigating other cross-coupling substrates and variants, Roush and coworkers also attempted to form the C2–C2' bond



Scheme 3.2 Roush's synthesis of the CDE-ring system and failed attempts to form the C2–C2' bond.

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[78] Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772.

via intramolecular oxidative phenolic coupling reactions without success.[79] The difficulty encountered in forming the C2–C2' bond was rationalized by the hindered environment surrounding the reactive sites, which contains substituents at each position *ortho* to C2 and C2', and the electron-rich nature of the naphthalene cross-coupling partners. This study demonstrated that forming the C2–C2' bond of the hibarimicins via a late-stage cross-coupling reaction would be difficult.

In 2003, Sulikowski and coworkers reported the synthesis of DE-ring system **20a**/**b** (Figure 3.5).[76b] **20a**/**b** was synthesized from dibenzofuran in eighteen steps and lacks the C2'–OMe substituent. Despite these shortcomings, the authors interestingly observed that the rotational barrier about the C2–C2' bond was dependent on the presence of the C1–OMOM group. More specifically, **20a**/**b** exist as a 1:1 mixture of atrop-diastereomers and fail to interconvert at temperatures up to 148 °C while des-MOM compounds **33a**/**33b** exhibited free rotation about their C2–C2' bonds at ambient temperature. The authors rationalize that rapid interconversion between atropisomers **33a** and **33b** can proceed via eclipsed conformation **34**, which is stabilized by π-electron overlap; this stabilization is apparently attenuated in **20**, which lacks a free phenol at C1. Although these model systems lack the critical C3'–OMe substituent, they suggested that the rotational barrier about the C2–C2' bond of a naphthazarin-naphthalene system may be influenced by the electronic nature of the C1-substituent.

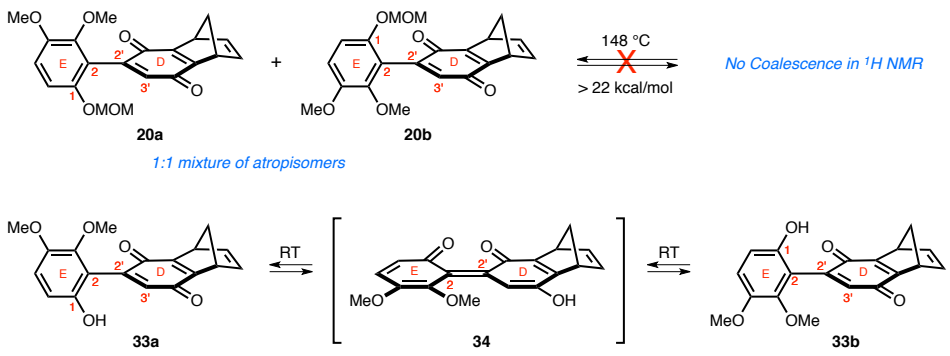
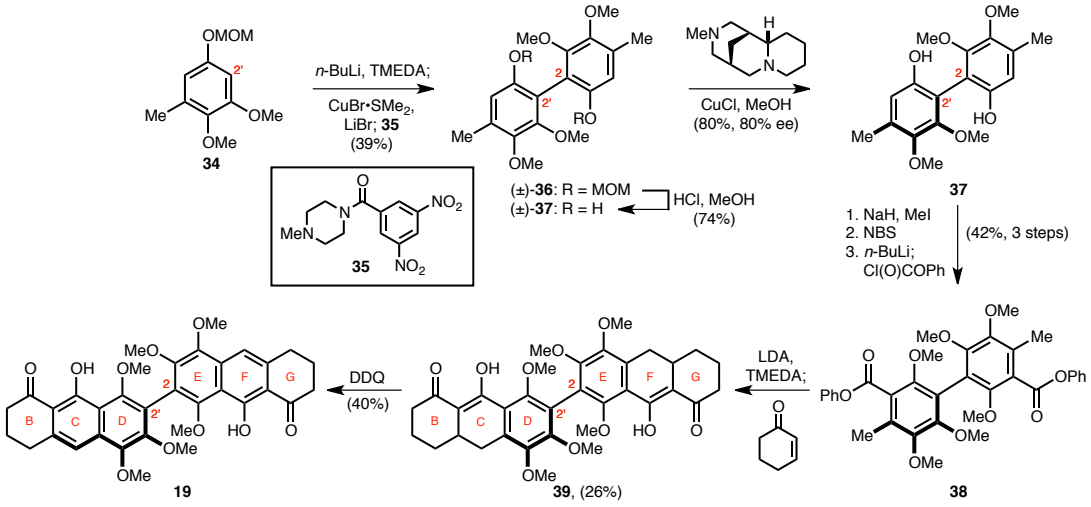


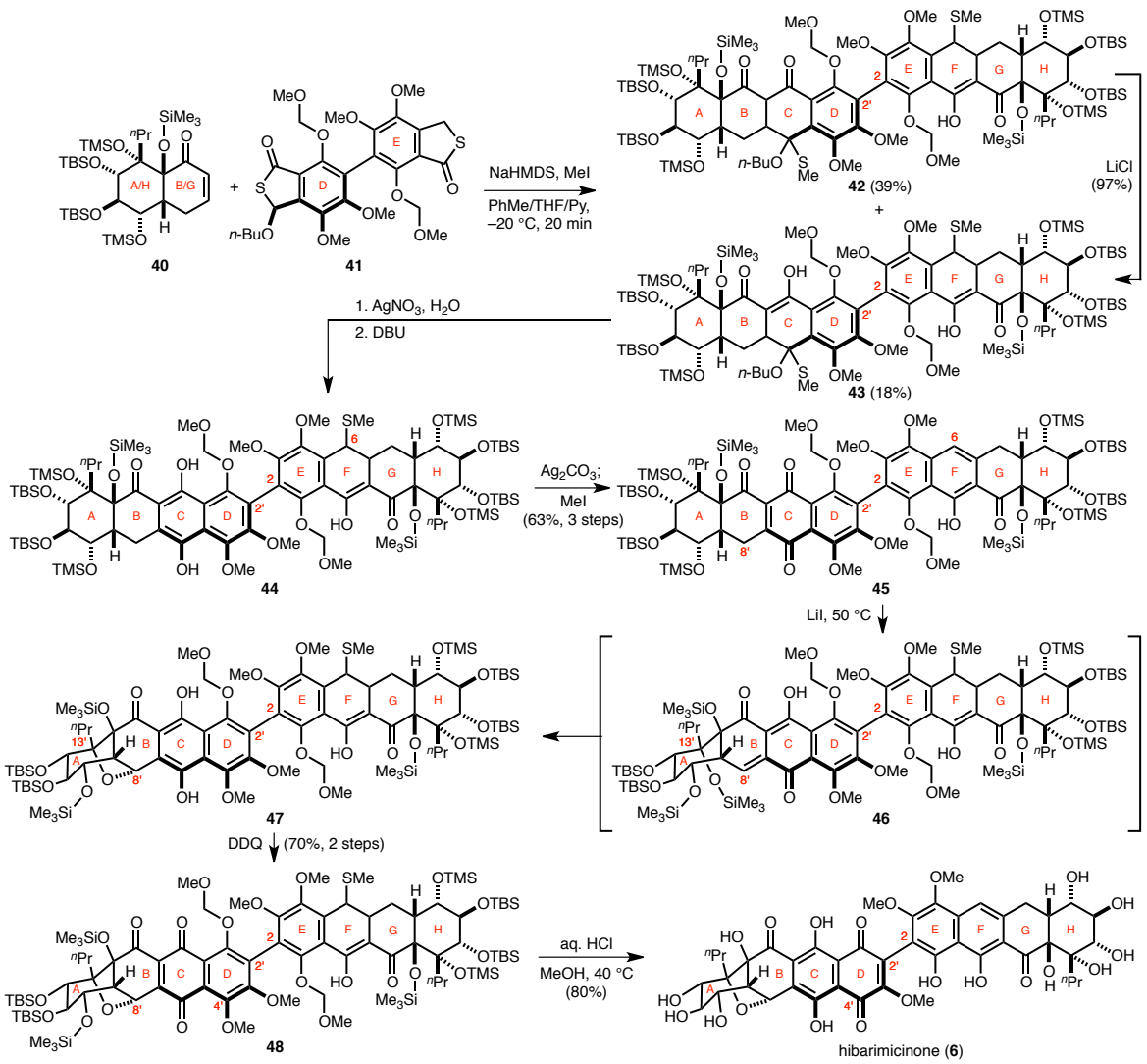
Figure 3.5 The C1-substituent influences the rotational barrier about the C2–C2' bond.

[79] Narayan, S. Ph.D. Thesis, University of Michigan, 2003.

Concurrent with our own studies, Sulikowski and coworkers reported the enantioselective synthesis of HMP-Y1 model system **19** using a bidirectional bis-Michael–Claisen reaction sequence (Scheme 3.3).[76i] The synthesis commenced with readily available trialkoxytoluene **34**, which was regioselectively lithiated at C2/C2' with *n*-butyllithium in the presence of TMEDA. Exposure of the resultant aryllithium intermediate to copper(I) bromide dimethylsulfide complex and lithium bromide, followed by a subsequent addition of amide **35** resulted in oxidative dimerization and formation of racemic biaryl **36**. Removal of the MOM groups afforded racemic biphenol **37**, which upon exposure to copper(I) complexed with O'Briens diamine was enriched to 80% ee by dynamic kinetic resolution. Enantioenriched **37** was then converted to bis-*o*-toluate **38** in three straightforward steps. The dianion of **38** was then formed by double deprotonation with LDA in the presence of TMEDA, and reacted with 2-cyclohexenone to generate the bis-Michael–Claisen reaction sequence product **39**. **39** was then oxidatively aromatized by DDQ to afford desired binaphthalene **19**. By comparing the CD-spectra of model system **19** with HMP-Y6 (**9**), Sulikowski and coworkers provided supporting evidence that the stereochemical configuration about the C2–C2' bond is indeed a*R* for **9**. This type of bidirectional synthesis strategy circumvents the need to form the hindered C2–C2' bond at a late-stage, but possesses its own challenges due to the idiosyncracies of anionic annulation reactions.



Scheme 3.3 A bidirectional double Michael–Claisen reaction sequence.



Scheme 3.4 Highlights from Tatsuta and coworker's total synthesis of hibarimicinone (**6**).

Concurrent with our own studies, Tatsuta and coworkers reported the first total synthesis of hibarimicinone (**6**) in early 2012. Uncannily, the bond disconnections that Tatsuta and coworkers utilized are identical to those that we had also contemporaneously developed and employed. The key steps and completion of the synthesis are outlined in Scheme 3.4. AB/HG-enone **40** and biaryl **41** were each prepared as single enantiomers by multi-step synthesis, which will not be discussed in the interest of brevity. Exposure of biaryl **41** to NaHMDS led to formation of the corresponding dianion, which reacted with two equivalents of enone **40** in an unsymmetrical bidirectional double annulation reaction to form a 1:1 mixture of 1,3-diketone **42** and dihydronaphthalene **43** after in situ methylation

of the intermediate bis-thiolate dianion. The unusual use of thiophthalides as aryl annulation partners critically required the use of pyridine as a co-solvent to suppress polymerization. This remarkable unprecedented transformation constructed the full carbon skeleton of hibarimicinone (**6**). **42** could be easily converted to **43** by treatment with lithium chloride.

Next, **43** was transformed to C-ring hydroquinone **44** by treatment with wet silver(I) nitrate and then subsequently with DBU. Treatment with silver(I) carbonate and iodomethane then promoted elimination of the C6-methylsulfide to aromatize the F-ring with concomitant oxidation of the C-ring to afford naphthazarin-naphthalene **45**. Exposure of **45** to LiI then promoted formation of *o*-quinone methide **46**, which was poised to undergo an etherification reaction with the proximal C13'-tertiary trimethylsilyether to rearomatize the C-ring and deliver nonacycle **47**. Although the authors make no comment, I had proposed that this reaction was biomimetic in nature and may in part reflect how HMP-Y1 (**8**) is biosynthetically converted to hibarimicinone (**6**) (vide infra). Reoxidation of the C-ring by DDQ then resulted in naphthazarin **48**, which upon treatment with hydrochloric acid in aqueous methanol led to global silyl group deprotection, demethylation of the C4'–OMe group, and concomitant transposition of the quinone from the C- to D-ring to afford hibarimicinone (**6**) in remarkable yield. No isomerization about the C2–C2' was documented.

This report was published approximately six months before our highly similar work was submitted for review. It is worth mentioning that despite the similarities between our syntheses and final intermediates, the conditions developed by Tatsuta and coworkers were not transferable to our system (vide infra). Furthermore, our ultimate goal was to not only prepare hibarimicinone (**6**) but eventually hibarimicin B (**2**) as well. Tatsuta's synthesis would require a very challenging final glycosylation of **6** or a later derivative since the carbohydrates are not compatible with the conditions required for C4'–OMe demethylation (i.e., acidic methanol).[73] This would be extremely challenging given the lability of the naphthalene-naphthazarin system, which easily isomerizes and cyclizes to give HMP-P1 (**10**) (vide infra). Nonetheless, Tatsuta's synthesis of hibarimicinone (**6**) was a landmark achievement and confirmed the molecule's absolute stereochemistry. The use of a

biomimetic etherification to install the C8'-ether bond allowed them to cleverly exploit the latent C_2-symmetry of **6** and employ a convergent bidirectional double annulation reaction to construct the full carbon skeleton in a one-pot operation.

II. Total Syntheses of HMP-Y1, Hibarimicinone, and HMP-P1

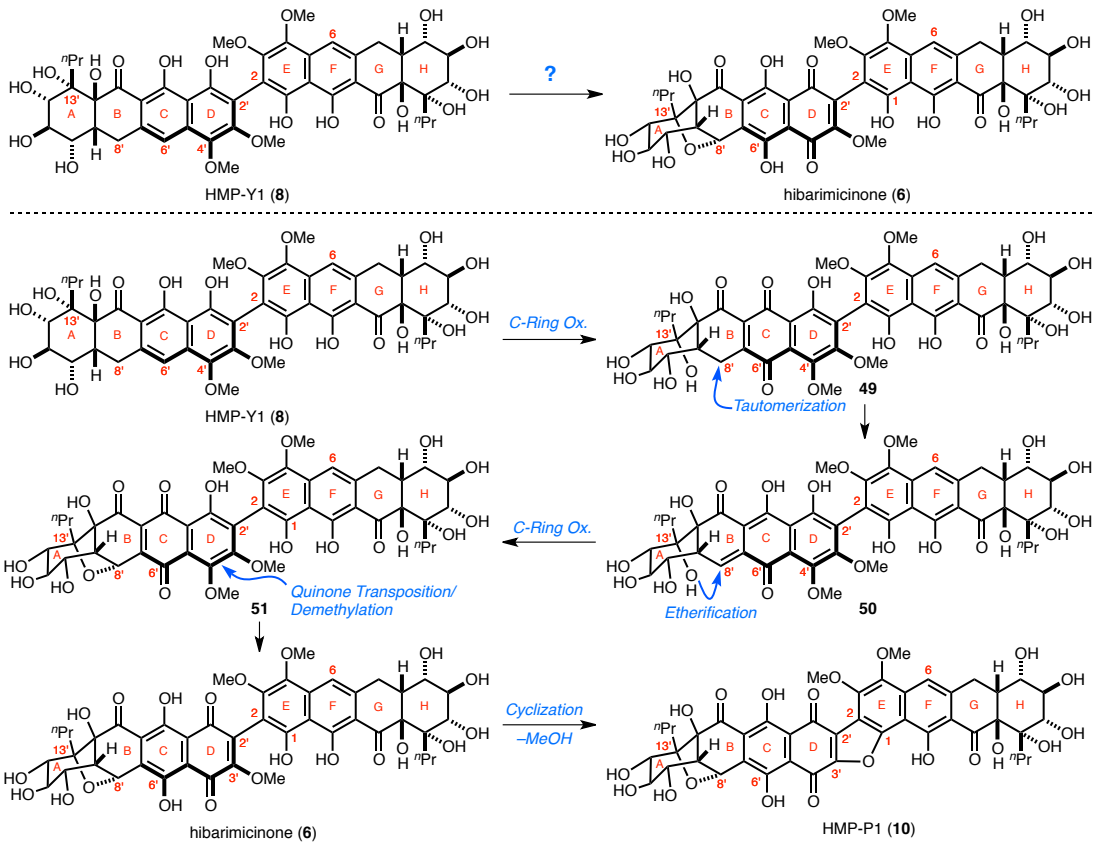
Chapter 4

Total Syntheses of HMP-Y1, Hibarimicinone, and HMP-P1

Introduction

As discussed in the introduction of chapter three, Hori and coworkers proposed a biosynthesis of the hibarimicins using evidence drawn from ^{13}C-labeled feeding and blocked mutant studies (Scheme 3.1). Importantly, they identified that the C_2-symmetric blocked mutant metabolite HMP-Y1 (**8**) is the precursor to hibarimicinone (**6**) (Scheme 4.1). However, no proposal for how this transformation might occur or via what possible intermediates was offered. Ostensibly, this conversion (**8** → **6**) proceeds by breaking the C_2-symmetry of **8** via oxidation of the B-, C-, and D-rings as well as demethylation of the C4'–OMe methyl group.

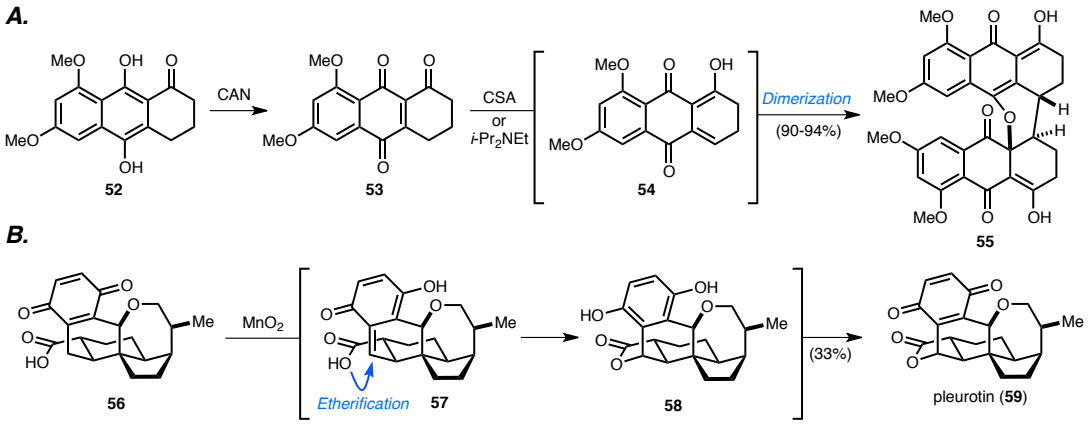
I postulated that a single desymmetrizing oxidation of the C-ring of **8** to hypothetical quinone **49** would be sufficient to *relay oxidation* to the B- and D-rings. This could be achieved via



Scheme 4.1 Our proposed biosynthetic conversion of HMP-Y1 (**8**) to hibarimicinone (**6**).

(1) tautomerization of quinone **49** to C8'-*o*-quinone methide **50**, (2) subsequent oxy-Michael addition of the C13'–OH to install the B-ring cyclic ether, (3) re-oxidation of the C-ring to give naphthazarin **51**, and (4) transposition of the C-ring quinone to the D-ring with concomitant chemoselective demethylation of the labile C4'–OMe group to give **6**. HMP-P1 (**10**) arises from **6** via cyclization of C1–OH onto C3' of the D-ring quinone and subsequent expulsion of methanol.

This proposal was compelling for several reasons. First, only a single oxidation (**8** → **49**) was needed to facilitate the introduction of all of the differential oxidation; this is in contrast to a previous proposal where three separate oxidations in the B-, C-, and D-rings occur relatively independently of one another. Second, there was substantial literature precedence that both formation of the C8'-*o*-quinone methide **50** and the subsequent oxy-Michael reaction would be feasible.[80] In their elegant synthesis of rugulosin, Nicolaou et. al. demonstrated that putative *o*-quinone methide **54** could be accessed from naphthazarin **53** under either mild basic or acidic conditions (Scheme 4.2A).[81] These species proved to be highly reactive, and **54** readily dimerized via a hetero-Diels-Alder reaction to afford heptacycle **55**. In another example, Hart and Huang found that treatment of quinone **56** with



Scheme 4.2 Related transformations utilizing *o*-quinone methide intermediates.

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[80] This analysis was before Tatsuta et. al. reported their synthesis of hibarimicinone (**6**).

[81] Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D. *J. Am. Chem. Soc.* **2007**, *129*, 4001–4013.

manganese dioxide triggered a sequence of reactions that led to formation of pleurotin (**59**).[82] This presumably occurs via initial tautomerization of **56** to *o*-quinone methide **57**, oxy-Michael addition by the pendant carboxylic acid to give hexacycle **58**, and reoxidation of the resultant hydroquinone to **59**.

We decided to embark on a total synthesis of hibarimicin B (**2**) due its structural complexity, promising biological activity, as well as the interesting potential mechanism of its biosynthesis. We were particularly interested in the proposed biosynthetic relay oxidation scheme discussed earlier in Scheme 4.1, and wondered if these transformations could be accomplished in the context of a biomimetic total synthesis. It is important to note that the carbohydrates are essential for the anti-proliferative effects of hibarimicin B (**2**),[72] and thus our ultimate goal was the total synthesis of **2**. However, an important milestone would be the synthesis of the aglycon, hibarimicinone (**6**), which is discussed in the upcoming sections.

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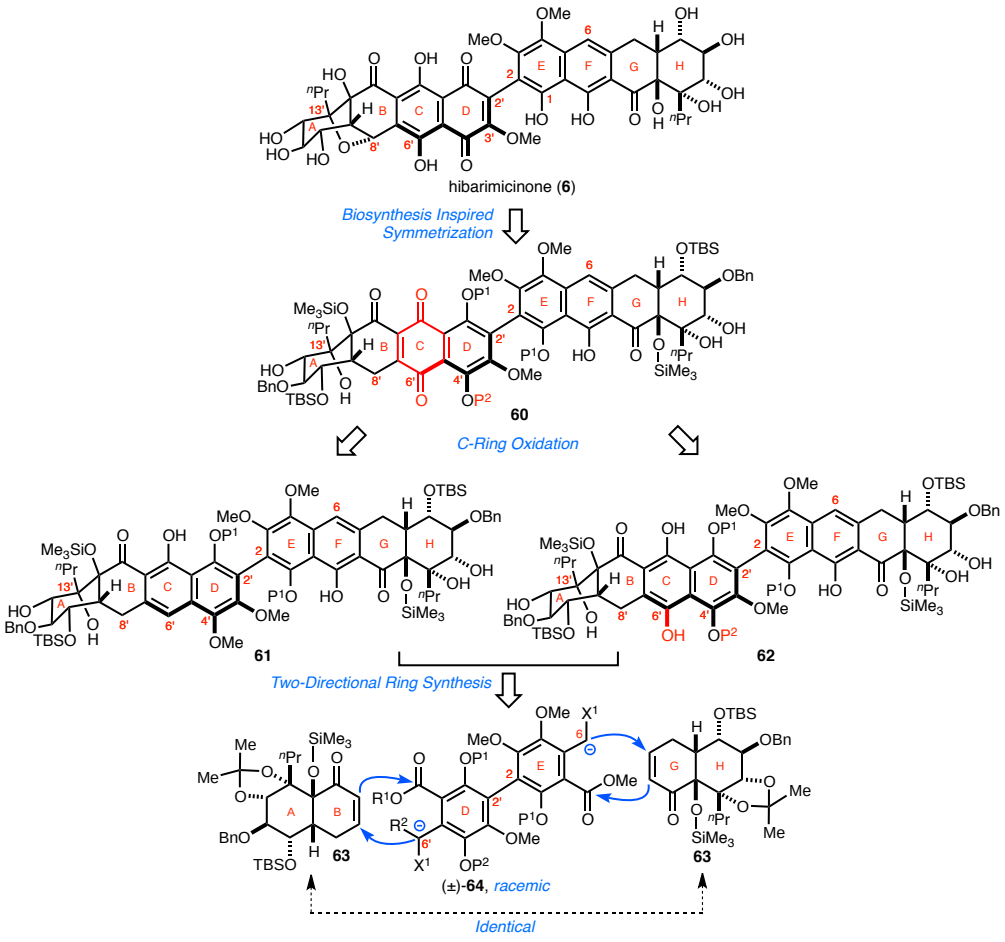
[82] Hart, D. J.; Huang, H.-C. *J. Am. Chem. Soc.* **1988**, *110*, 1634–1635.

Synthesis Plan

Inspired by our biosynthetic relay oxidation hypothesis, we envisioned that a similar set of biomimetic retrosynthetic disconnections could simplify hibarimicinone (**6**) to quinone **60**. In the forward sense, this would involve: (1) tautomerization of quinone **60** to the corresponding C8'-*o*-quinone methide with subsequent oxy-Michael addition of the C13'–OH to install the B-ring cyclic ether, (2) re-oxidation of the C-ring, and (3) transposition of the C-ring quinone to the D-ring to give **6** (i.e., Scheme 4.1: **49** → **50** → **51** → **6**). We imagined that **60** could be accessed from two possible precursors, C_2-symmetric octacycle **61**, and pseudo-C_2-symmetric octacycle **62**. Targeting **61** was attractive for two reasons: (1) global deprotection would yield HMP-Y1 (**8**) and (2) it would allow us



Scheme 4.3 Synthesis plan for hibarimicinone (**6**) and HMP-Y1 (**8**).

to directly assess the feasibility of a biomimetic mono-oxidation to access quinone **60**. In contrast to **61**, the C_2-symmetry of **62** is perturbed by the presence of the C6'–OH and potentially a non-methylether protecting group at C4' (both highlighted in red). The C6'–OH was included to facilitate chemoselective C-ring oxidation to quinone **60**, obviating the need for a desymmetrizing mono-oxidation. The potential use of a non-methylether protecting group at C4' (e.g., a benzyl group) was a strategic consideration to protect the sensitive naphthalene-naphthazarin core up until the last step of an eventual synthesis of hibarimicin B (**2**), without requiring a harsh C4'–OMe demethylation that would be ultimately incompatible with the carbohydrates.

The most noteworthy feature shared by both **61** and **62** is the degeneracy of the AB- and HG-ring systems that result from the retrosynthetic excision of the B-ring cyclic ether bond. Exploiting this degeneracy, it was next envisioned that both octacyclic systems could be constructed in single operations via a bidirectional double annulation, where the dianion of biaryl **64** would react with two equivalents of the AB/HG-enone **63**. The use of a symmetric biaryl would lead to **61** whereas the employment of an unsymmetrical variant with additional oxidation at C6', would result in **62**. Both of these strategies are convergent and avoid constructing the hindered C2–C2' bond at a late stage.[83] At the outset of our studies, the configuration of the C2–C2' stereochemical axis of hibarimicinone (**6**) was only assigned based on its CD-spectra. Consequently, we elected to proceed with racemic biaryl **64** to rigorously prepare and characterize both atropisomers of HMP-Y1 (**8**) and hibarimicinone (**6**).

The next sections of this chapter describe: (1) completion of the *ent*-AB/HG-enone, (2) syntheses of the monomeric ABCD- and EFGH-ring systems and demonstration of a biomimetic etherification reaction, (3) completion of HMP-Y1 (**8**) and attempted desymmetrizing mono-oxidation, (4) completion of hibarimicinone (**6**) via an unsymmetrical bidirectional annulation, and (5) conversion of **6** to HMP-P1 (**10**) and discovery of a pH-dependent rotational barrier about the C2–C2' bond of **6**. It is important to acknowledge that the synthesis of the *ent*-AB/HG-enone was

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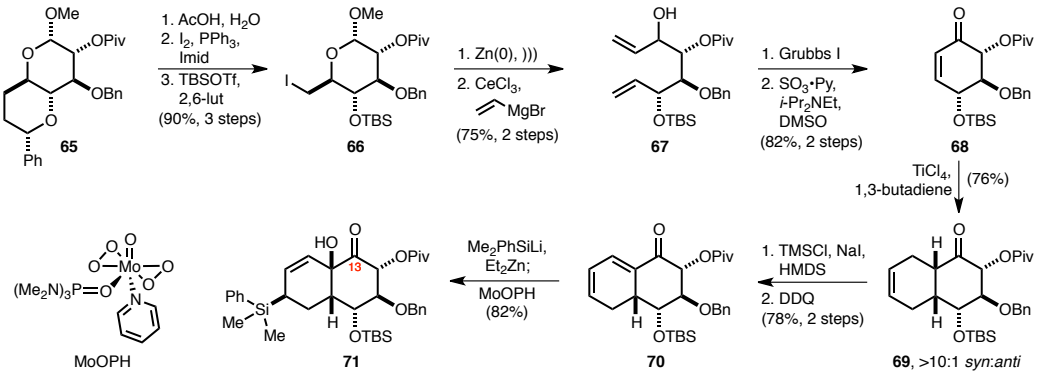
[83] As discussed earlier, efforts by the Roush group to form the C2–C2' bond in simple model systems via cross-coupling were met with considerable difficulty (Scheme 3.2).

predominantly the work of my coworker, Mr. Benjamin Milgram. Our efforts then diverged as B. Milgram worked on the synthesis of the carbohydrates of hibarimicin B (**2**) while I performed the work presented in this document concerning the synthesis of the natural product aglycons, except where noted. Lastly, the aforementioned sections do not follow any particular chronological order, but are divided in a way to facilitate ease of discussion.

Completion of the *ent*-AB/HG-Enone

Our discussion begins with the synthesis of AB/HG-enone **63**, a requisite building block for not only the ultimate synthesis of the hibarimicin aglycons but for crucial monomeric model studies investigating key transformations. At the outset of our synthetic studies, we were uncertain of the absolute stereochemistry of hibarimicin B (**2**).[84] B. Milgram, who initiated the AB/HG-enone synthesis, targeted the enantiomer of AB/HG-enone **63** (*ent*-**63**), which unfortunately corresponded to the unnatural enantiomer of hibarimicinone (**6**). This problem would later be rectified by synthesis of the correct enantiomer, but the AB/HG-enone and hibarimicinone (**6**) were in fact synthesized as the unnatural enantiomers first. In the interest of brevity, only the correct enantiomeric series will be discussed unless the experiments were only accomplished with the unnatural enantiomeric series.



Scheme 4.4 B. Milgram's synthesis of bicyclic ketone **71**.

I joined the AB/HG-enone synthesis at a fairly advanced stage of its development. B. Milgram had accessed bicyclic ketone **71**; the final, optimized route to **71** is summarized in Scheme 4.4. In the interest of brevity and collegiality, the details of this work will not be discussed here.[85] After bringing up material to the forefront, my first contribution involved the addition of an *n*-propyl organometallic species to the C13-ketone of **71**. I found that careful addition of **71** to a mixture of *n*-

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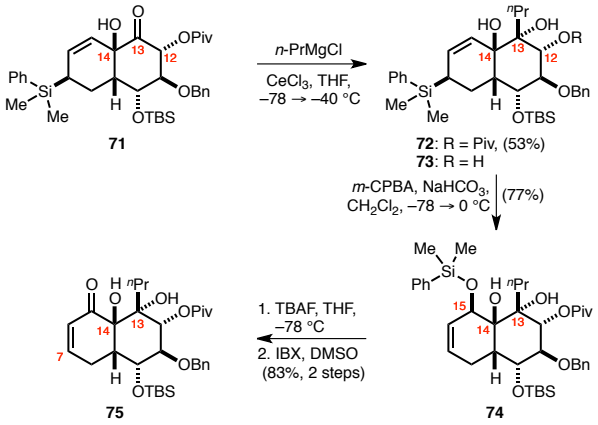
[84] Although Hori and coworkers had tentatively assigned the absolute stereochemistry of hibarimicin B (**2**), this crucial paper (in Japanese) was unfortunately unbeknownst to us at the time. See ref. 74.

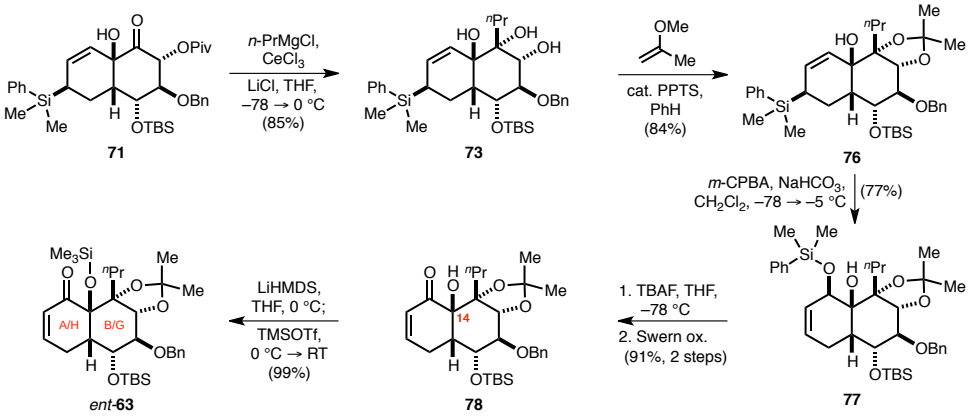
[85] For a full discussion, see: Milgram, B. C.; Liau, B. B.; Shair, M. D. *Org. Lett.* **2011**, *13*, 6436–6439.

propylmagnesium chloride and cerium(III) chloride at –78 °C, followed by gradual warming to –40 °C, afforded the desired *n*-propyl adduct **72** as a single diastereomer (Scheme 4.5). Longer reaction times or warmer temperatures led to significant amounts of pivaloyl ester cleaved product **73**, an observation that would prove to be important later on (vide infra). The free C14-tertiary hydroxyl of **71** was crucial to the success of this reaction, as B. Milgram had previously found that additions to the C14-TMS derivatives only afforded hydride reduction products. Next, I found that treatment of **72** with *m*-CPBA led to allylic silyl ether **74**. This transformation presumably occurs via epoxidation of the allylic silane, followed by in situ β-silicon promoted epoxide opening with concomitant 1,4-transfer of silicon to the newly formed C15-secondary hydroxyl. Exposure of **74** to TBAF at –78 °C led to chemoselective removal of the dimethylphenylsilyl group, and the resultant allylic alcohol was oxidized with IBX to give desired AB/HG-enone **75**. Unfortunately, attempts to protect the C13-tertiary hydroxyl of **74** and **75** proved futile due to problems with poor reactivity or cyclization of the C13-tertiary hydroxyl onto C7, respectively. Since protection of the C13-tertiary hydroxyl was most likely critical for the ensuing anionic annulation reactions, a revised protecting group scheme was needed.



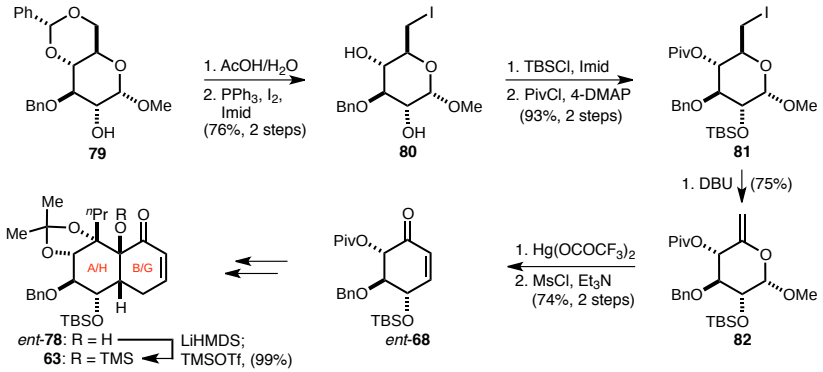
Scheme 4.5 Synthesis of AB/HG-enone **75**.

I postulated that if the pivaloyl ester of **72** were purposefully removed, then a cyclic protecting group could be used to protect the otherwise inaccessible C13-tertiary hydroxyl by first attaching to the less hindered C12-secondary hydroxyl of **73**. This strategy would also avoid the deprotection of the pivaloyl ester at a later stage in the synthesis, which we predicted to be challenging. B. Milgram found that addition of **71** to a mixture of *n*-propylmagnesium chloride, cerium chloride, and lithium chloride at –78 °C, followed by warming to 0 °C, facilitated formation of diol **73** in good yield (Scheme 4.6). With **73** in hand, I found that the diol could be protected using 2-methoxypropene to afford acetonide **76**. Similarly as before, treatment of **76** with *m*-CPBA led to allylic dimethylphenylsilyl ether **77**. Exposure of **77** to TBAF and subsequent oxidation of the resultant allylic alcohol under Swern conditions gave desired enone **78**. During the course of the subsequent annulation studies, I found that protection of the C14-tertiary hydroxyl was critical, and this was accomplished by deprotonation of **78** with LiHMDS, followed by silylation with TMSOTf, to yield fully protected *ent*-AB/HG-enone *ent*-**63**.



Scheme 4.6 Completion of fully protected *ent*-AB/HG-enone *ent*-**63**.

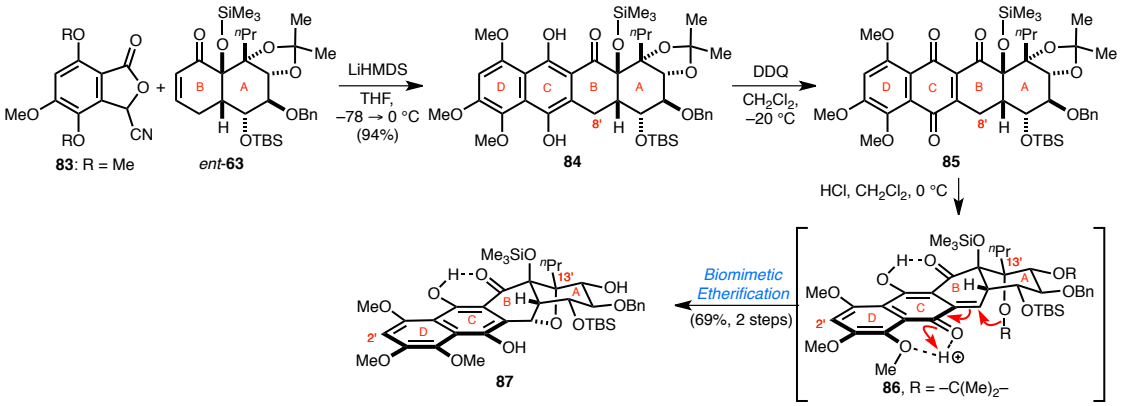
As mentioned earlier, the absolute stereochemistry of *ent*-AB/HG-enone *ent*-**63** corresponds to the unnatural enantiomer of hibarimicinone (**6**). The AB/HG-enone **63** with stereochemistry corresponding to the natural enantiomer of **6** was ultimately prepared from key intermediate cyclohexenone *ent*-**68** following an analogous series of diastereoselective transformations. The synthesis of *ent*-**68** was developed and executed by B. Milgram, and for the reader's interest, is briefly outlined in Scheme 4.7.



Scheme 4.7 B. Milgram's synthesis of the correct enantiomer of the AB/HG-Enone **63**.

Synthesis of the ABCD- and EFGH-Ring Systems of Hibarimicinone

With AB/HG-enone in hand, a model ABCD-ring system was investigated to test the viability of our proposed late-stage biomimetic etherification to construct the pentacyclic western half of hibarimicinone (**6**). Kraus annulation[86] of cyanophthalide **83**[87] with *ent*-AB/HG-enone *ent*-**63** under rigorously oxygen-free conditions afforded ABCD-tetracycle **84** (Scheme 4.8).[88] Deoxygenation was critical for the success of the annulation, as adventitious oxygen resulted in decomposition. **84** was then oxidized by DDQ to the corresponding C-ring quinone **85**. Fortuitously, I discovered that exposure of **85** to anhydrous hydrochloric acid afforded pentacycle **87** in 69% yield from **84**. As discussed earlier, this transformation presumably occurs through the intermediacy of *o*-quinone methide **86**, which is trapped by the proximal acetonide oxygen with concomitant acetonide cleavage. Notably, this acid-mediated etherification required high dilution in order to avoid formation of **84** and decomposition products, potentially via intermolecular processes. Acetonide cleavage was most likely



Scheme 4.8 Synthesis of a model ABCD-pentacyclic system.

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[86] Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett*. **1978,** *19*, 2263-2266.

[87] **83** was prepared according to Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc*. **1994**, *116*, 9921–9926.

[88] The Kraus annulation could be accomplished equally well with derivatives of **83** where R = MOM or R = Bn.

triggered by its proximity to the reactive *o*-quinone methide intermediate as suggested by the failure to isolate any acetonide cleavage products that lack the cyclic ether bond. This is further supported by later observations on the dimeric system, where only the acetonide of the A-ring is cleaved whereas the H-ring acetonide remained intact (vide infra, Scheme 4.16). Overall, the model oxidation-etherification sequence afforded excellent precedence for subsequent studies.

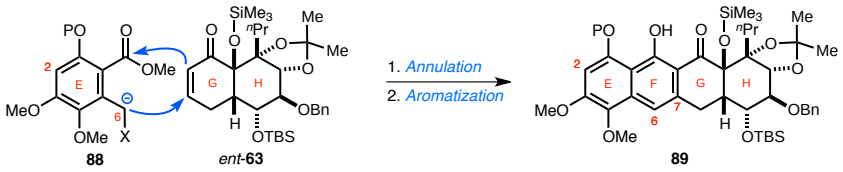

Figure 4.1 Michael–Claisen reaction sequence to construct the EFGH-ring system.

Concurrently, I pursued model studies investigating the Michael–Claisen reaction sequence to construct the EFGH-ring system **89** (Figure 4.1). These studies were particularly crucial due to the lack of robust annulation sequences to generate naphthols (1-hydroxynaphthalenes rather than 1,4-dihydroxynaphthalenes, i.e., hydroquinones).[89] The ultimate success of Michael–Claisen reaction sequences[90] hinges on numerous factors. These include, but are not limited to: (1) the stability and nucleophilicity of the reacting carbanion,[91] (2) the stability of the electrophilic acceptor to the base required to deprotonate the donor,[92] and (3) the steric bulk of the annulation donor (substituents at

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[89] For reviews, see: (a) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892–1918. (b) Rathwell, K.; Brimble, M. A. *Synthesis* **2007**, *5*, 643–662.

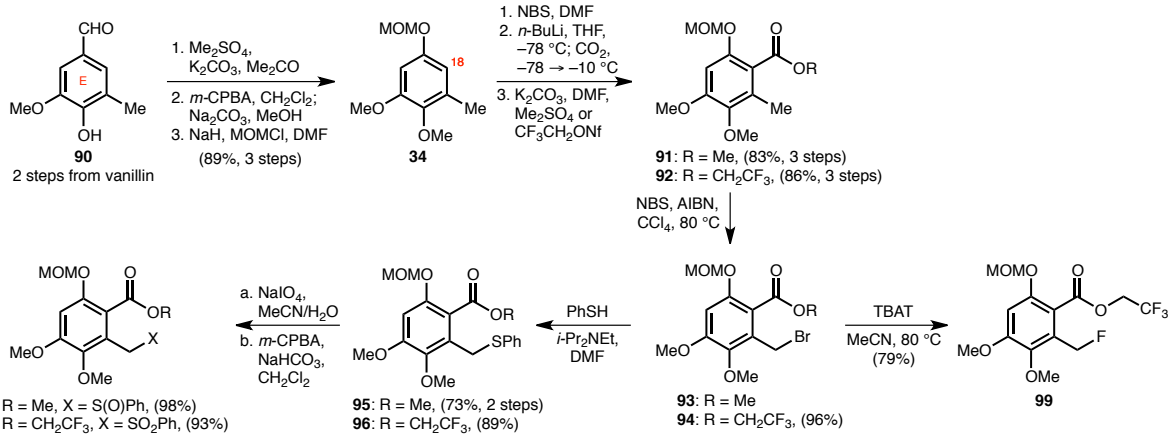
[90] For other uses of Michael–Claisen reaction sequences to construct naphthalene derivatives, see: Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–17927, and references therein.

[91] (a) *o*-Toluate and related carbanions will suffer from competitive bimolecular self-condensation reactions with the ester moiety if the Michael addition is not fast enough. See Brubaker, J. D. Ph.D. Thesis, Harvard University, 2007 and references therein. (b) In the case of a single annulation process, the instability of the deprotonated annulation donor can often be partially circumvented through the use of excess donor. However, due to the inherent stoichiometry of the bidirectional double annulation, the biaryl donor is used as the limiting reactant and thus the stability of its dianion is critical to the success of the reaction

[92] *ent*-**63** is stable to LiTMP and LDA at –78 °C, and to LiHMDS at 0 °C in THF. At higher respective temperatures for prolonged reaction times, significant decomposition occurred.

C6/C6' and the ester side chain) and of the annulation acceptor. Furthermore, the slow step of the tandem reaction sequence will change based on the particular donor and acceptor used. Due to these challenges, numerous strategies were pursued with different substituents at C6 to stabilize the benzylic anion **88** and provide a functional group handle to later introduce the required C6–C7 unsaturation.

The syntheses of the E-ring aryl donors began with 5-methylvanillin **90**[93] (Scheme 4.9), which was converted to trialkoxytoluene **34** in a three step process involving: (1) *O*-methylation, (2) Dakin oxidation followed by in situ formate methanolysis, and (3) MOM protection of the resultant phenol. Regioselective electrophilic aromatic bromination of **34** at C18, followed by lithium-halogen exchange and trapping of the resultant aryllithium species with carbon dioxide, afforded the corresponding benzoic acid. Next, this acid could either be methylated or trifluoroethylated to obtain *o*-toluates **91** or **92**. Benzylic radical bromination, followed by displacement with the appropriate nucleophile and oxidation as needed, then afforded the various E-ring aryls used in our studies.



Scheme 4.9 Synthesis of E-ring aryl donors.

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[93] 5-Methylvanillin (**90**) was prepared from vanillin in two steps on multigram scale following a literature procedure: Sinhababu, A. K.; Borchardt, R. T. *Syn. Comm.* **1983**, *13*, 677–683.

o-Toluate **91** was the first E-ring aryl donor to be investigated. I soon determined that the desired Michael–Claisen reaction sequence was efficiently accomplished with 2-cyclohexenone **100**[94] to afford dihydronaphthalene **101** (Scheme 4.10A). The aromatization of **101** could be accomplished by oxidation with DDQ, but difficulties with over-oxidation to the corresponding juglone were problematic.[95] The remaining results of the Michael–Claisen reaction sequence study with model E-ring aryl donors are summarized in Scheme 4.10B. Reaction of benzylic sulfoxide **97** with *ent*-**63** in the presence of LiHMDS directly afforded desired EFGH-naphthol **89** in moderate yield.[96] Quite peculiarly, **89** and more polar products (TLC analysis)—presumably either Michael adducts or Michael–Claisen product **103**—were formed rapidly and simultaneously upon warming to 0 °C (ca. 1 h), but no further conversion of these products to **89** was observed over several hours. This perhaps suggests that the Michael–Claisen reaction sequence is not diastereoselective[97] and that **89** arose from the only diastereomer of **103** that can undergo *syn*-elimination. Additionally, significant amounts of starting materials *ent*-**63** and **97** (ca. 50%, TLC analysis) also remained at this time. The presence of unreacted starting material despite the rapid formation of **89** suggested that only one enantiomer of racemic sulfoxide **97** reacted facilely with *ent*-**63**.[98] Despite the relative success of the benzylic sulfoxide annulation, which directly afforded the aromatized F-ring, we continued to explore alternative annulations due to the challenging nature of our upcoming bidirectional double annulations.

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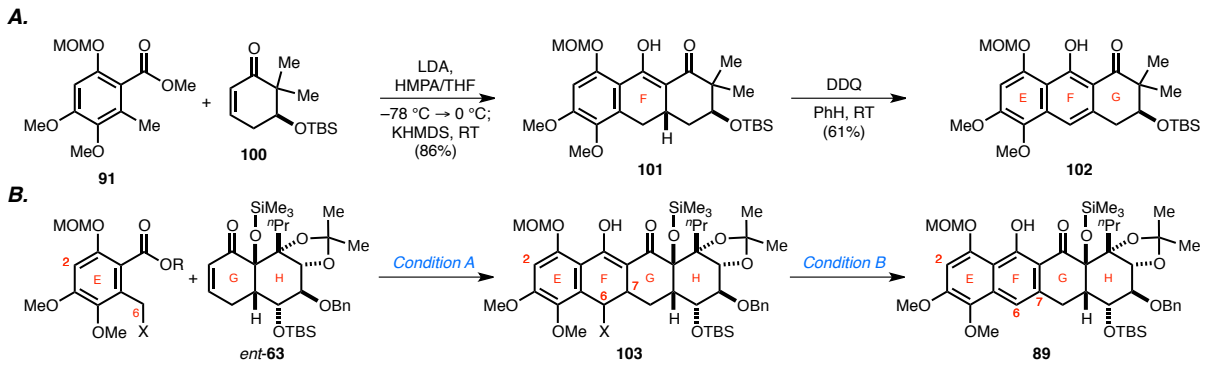
[94] Model cyclohexenone **100** was used since this study preceded synthesis of *ent*-**63**.

[95] Alternatively, heating **101** in the presence of phenylselenyl chloride and pyridine also facilitated aromatization of the F-ring.

[96] For other examples of benzylic sulfoxide annulations, see: (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180. (b) Lee, H. G.; Ahn, J.-Y.; Lee, A. S.; Shair, M. D. *Chem. Eur. J.* **2010**, *16*, 13058–13062.

[97] This is consistent with results from other Michael–Claisen reaction sequences with *ent*-**63**.

[98] These suspicions were later confirmed with observations in our unsymmetrical bidirectional annulation studies (vide infra).



Aryl	X	R	Condition A	Condition B	Yield of 89[99]
97	S(O)Ph	Me	LiHMDS, THF, –78 → 0 °C	N/A	48%
98	SO_2Ph	CH_2CF_3	LiHMDS, THF, –78 → 0 °C	$NaHCO_3$, xylenes, 140 °C	29-54%
96	SPh	CH_2CF_3	LiHMDS, THF, –78 → 0 °C	$AgBF_4$, DTBMP, CH_2Cl_2, RT	87%
99	F	CH_2CF_3	LiTMP, THF, –78 °C; HMDS, –78 → 0 °C	$NaHCO_3$, TFE, 80 °C	83%

Scheme 4.10 Michael–Claisen reaction sequence studies to construct the model EFGH-ring system.

Next, reaction of benzylic sulfone **98** with *ent*-**63** in the presence of LiHMDS afforded a complex mixture of diastereomers of presumably annulated products **103**.[100] After some investigation, I found that heating the mixture of products to 140 °C in xylenes with sodium bicarbonate promoted elimination of phenylsulfinic acid to afford desired **89**, albeit in low to moderate yield. Benzylic sulfide **96** was also a competent partner and underwent annulation with *ent*-**63** at 0 °C using LiHMDS as base. Fortunately, aromatization to **89** could also be achieved in high yield through the use of silver(I) tetrafluoroborate as a thiophilic Lewis acid and DTBMP as a non-coordinating proton scavenger.[101]

Lastly, I had also envisaged that a benzylic fluoride Michael–Claisen reaction sequence could generate naphthalenes after subsequent dehydrohalogenation. Although there was no precedence for

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[99] Isolated yield over two steps.

[100] For other examples of benzylic sulfone annulations, see: (a) Wildeman, J.; Borgen, P. C.; Pluim, H. *Tetrahedron Lett*. **1978**, *25*, 2213–2216. (b) Huang, X.; Xue, J. *J. Org. Chem*. **2007**, *72*, 3965–3968.

[101] The use of silver(I) salts to aromatize the F-ring was eventually replaced with DMTSF in the unsymmetrical bidirectional annulation studies (vide infra).

such a strategy, a benzylic fluoride annulation donor was attractive for several reasons: (1) the electronegative fluorine atom should stabilize the aryl anion, (2) the small atomic radius of fluorine should provide minimal steric hinderance to the initial Michael reaction, (3) the strength of C–F bonds would disfavor α-elimination and S_N2 displacement of fluoride, and (4) despite the strength of C–F bonds, elimination of the benzylic fluoride under appropriate conditions could lead to C- and F-ring aromatization.[102] To our satisfaction, annulation of benzylic fluoride **99** with *ent*-**63** was facilitated by addition of LiTMP at –78 °C, followed by subsequent addition of HMDS and warming to 0 °C, affording dihydronaphthalene **103** as a mixture of diastereomers. I then discovered that simple heating of the crude mixture of **103** in TFE promoted formal elimination of HF to yield EFGH-ring system **89**. In contrast to the other annulation reactions described, the use of a benzylic fluoride allowed the initial Michael reaction to occur at –78 °C, thus minimizing potential decomposition of the corresponding biaryl donor (vide infra). The employment of a benzylic fluoride annulation-elimination sequence to generate naphthalene derivatives is without precedence and may prove to be a general method for the synthesis of naphthols.

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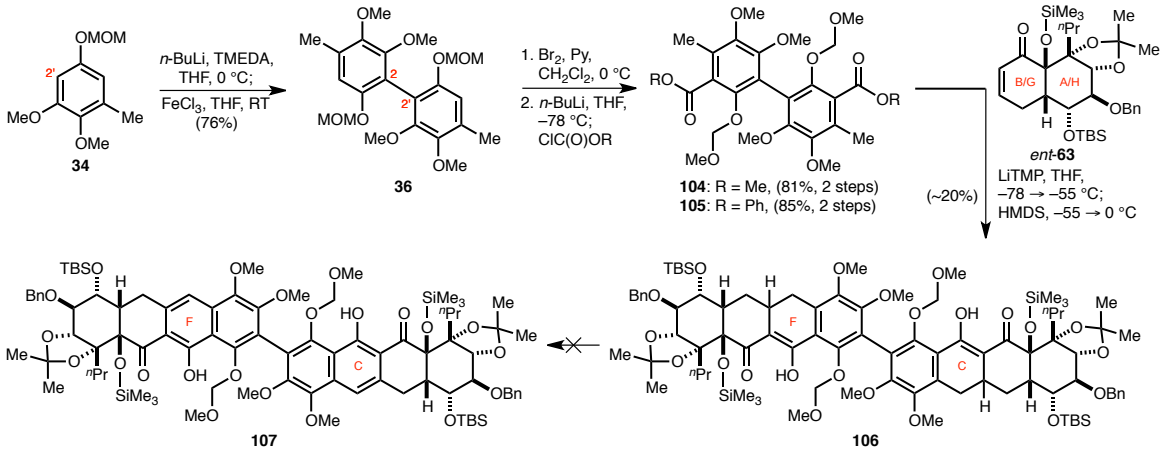
[102] Bitha, P.; Hlavka, J. J.; Boothe, J. H. *J. Med. Chem.* **1970**, *13*, 89–92.

Synthesis of HMP-Y1 and an Oxidative Desymmetrization Approach toward Hibarimicinone

With model systems established for constructing the monomeric eastern and western halves of hibarimicinone (**6**), the synthesis of their dimeric counterparts will now be discussed. Our synthesis plan for HMP-Y1 (**8**) involved a symmetric bidirectional double annulation to generate the C_2-symmetric octacyclic skeleton (Scheme 4.3). Such an ambitious strategy required a flexible synthesis of symmetric biaryl annulation donors in which different substituents at C6/C6' could be introduced. The biaryl synthesis commenced with regioselective *o*-lithiation of **34** at C2' and $FeCl_3$-mediated oxidative dimerization of the resultant aryllithium species delivered racemic biaryl **36** (Scheme 4.11). The ester groups were then installed in a two-step sequence involving bromination and lithium–halogen exchange, followed by acylation, to afford either bis-methylester **104** or bis-phenylester **105**.

We found that **104** could be deprotonated twice by LiTMP and that the corresponding dianion seemed to undergo the bidirectional bis-Michael–Claisen reaction sequence with the AB/HG-enone *ent*-**63** (Scheme 4.11). However, the slow rate of both the Michael and Claisen reactions[103] of



Scheme 4.11 Synthesis of bis-*o*-toluates and attempted double Michael–Claisen reaction sequences.

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[103] Simple 2-cyclohexenones will undergo the Michael addition within seconds at –78 °C and eventual Claisen reaction at –10 °C with the *o*-toluate carbanion corresponding to the D/E-ring (Scheme 4.10: **100** → **101**). In contrast, *ent*-**63** underwent Michael addition after approximately 1 h at –78 °C and the Claisen reaction could never be driven to completion with the dianion of **104**.

the sequence with sterically encumbered *ent*-**63** led to minor amounts of the desired octacyclic dihydronaphthalene products **106**. Attempts to facilitate the Claisen step of the reaction sequence by using activated phenylester **105** were somewhat successful, but other problems arose since the sterically larger activated esters slowed the initial Michael reaction and the dianions were more prone to decomposition. Most importantly, aromatization of the C/F-rings of **106** using my previously developed conditions was met with difficulty and led us to consider alternative approaches.

We next envisioned that our newly discovered benzylic fluoride Michael–Claisen reaction sequence could be employed to form the binaphthalene core of HMP-Y1 (**8**). The dianion of **104** was brominated with $(BrCF_2)_2$ to yield the bis-benzylic bromide, which upon heating with TBAT[104] afforded bis-benzylic fluoride **108** (Scheme 4.12). After significant experimentation, the desired protected HMP-Y1 derivatives **107a** and **107b**[105] were accessed from **63** and **108** in a two-step procedure involving: (1) a bis-Michael–Claisen reaction sequence promoted by LiTMP and $MgBr_2 \bullet OEt_2$ to afford octacycles **109a** and **109b** and (2) the formal elimination of hydrofluoric acid by heating the crude reaction products in TFE to achieve aromatization of the C/ F-rings and provide atropisomers **107a** and **107b**, which were readily separated and carried forward independently. Several features of this sequence deserve comment. As I had hoped, the use of a bis-benzylic fluoride **108** allowed for the initial bis-Michael addition to occur at –78 °C, thus minimizing decomposition of the dianion intermediate and of **63**. Addition of $MgBr_2 \bullet OEt_2$ mid annulation sequence was critical to promote the final intramolecular Claisen reactions and obviated the need to use an activated ester analog. This discovery should help expand the substrate scope of the Michael–Claisen reaction sequence. Finally, the unique ability of TFE to promote the desired elimination is presumably due to its ability to strongly hydrogen bond with fluorine, and thus activate it for mild solvolysis. Indeed, use of ethanol in place of TFE only led to trace elimination.

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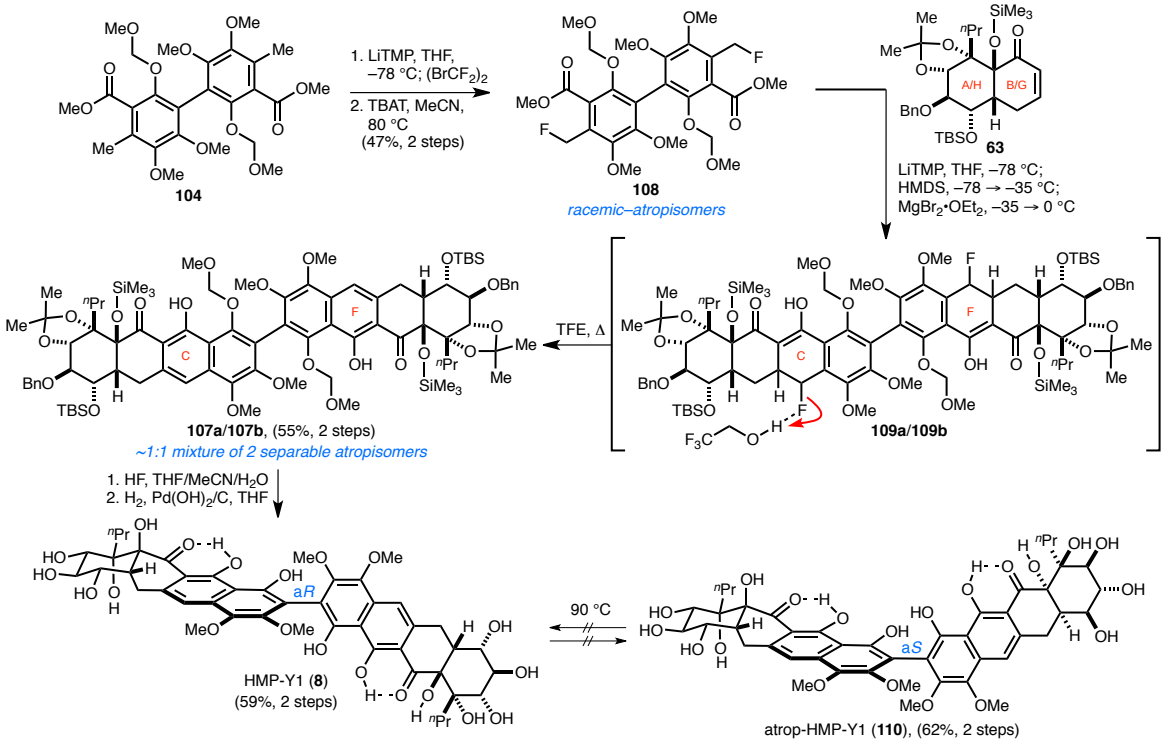
[104] Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167.

[105] For brevity, each atropisomer is depicted as a single structure lacking stereochemistry about the C2–C2' bond. See Experimental Section for full details.



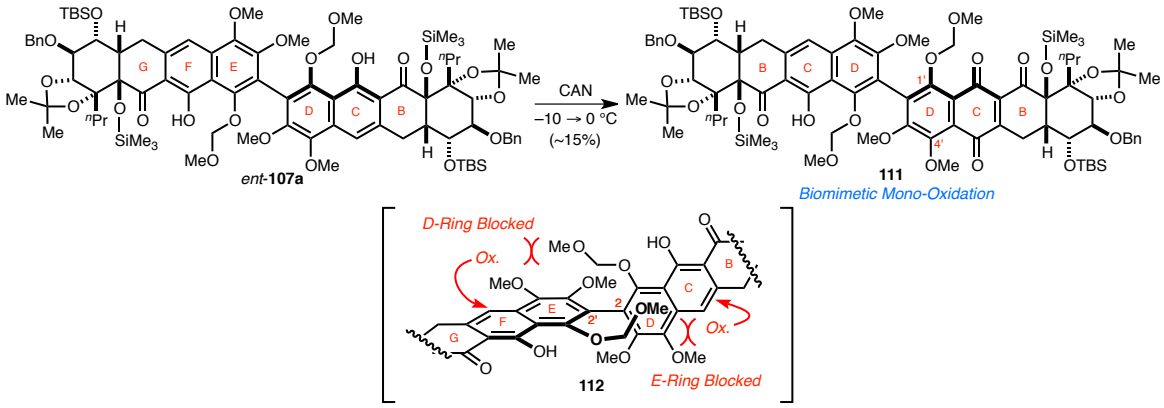
Scheme 4.12 Development of a benzylic fluoride Michael–Claisen reaction sequence to achieve the first total syntheses of HMP-Y1 (**8**) and atrop-HMP-Y1 (**110**).

B. Milgram optimized the global deprotection of **107a** and **107b** in the correct enantiomeric series, which was accomplished with aqueous hydrofluoric acid followed by hydrogenolysis to afford HMP-Y1 (**8**) and atrop-HMP-Y1 (**110**), respectively.[106] B. Milgram also demonstrated that heating **8** or **110** to 90 °C led to no detectable isomerization about the C2–C2' bond. With no authentic CD-spectra for natural **8** available, synthetic **8** and **110** were designated based on comparison of their CD-spectra with the CD-spectrum of the glycosylated derivative of **8**, HMP-Y6 (**9**).[76i] As discussed in the previous chapter, the axial stereochemistry of **8** has not been rigorously determined, although model studies and the CD-spectra of **9** and hibarimicinone (**6**) suggest that **8** possesses the a*R* configuration by the CD exciton chirality method.[76i] Additionally, **8**, **6**, and hibarimicin A–G are all isolated as single atropisomers. We have shown that the axial stereochemistry of **8** and **6** are not the result of

[106] No NMR or CD spectra for HMP-Y1 (**8**) have been previously recorded according to a personal communication with H. Hori and Y. Igarashi.

thermodynamic equilibration (vide infra), and thus their biosynthetic relationship also argues that they possess the same relative configuration about the C2–C2' bond. Therefore, since the axial chirality of **6** was unambiguously determined,[77] **8** was assigned the a*R* configuration.

With a route to protected derivatives of HMP-Y1 (**8**) and atrop-HMP-Y1 (**110**) established, I next attempted the biomimetic mono-oxidation. I discovered that the desired oxidation of *ent*-**107a** to the C-ring quinone **111** could be achieved in low yield with CAN (Scheme 4.13), demonstrating the plausibility of our proposed biomimetic desymmetrizing oxidation. We speculated that the congested biaryl may sterically occlude the approach of oxidants to the otherwise easily oxidized D/E-ring system,[107] allowing oxidation of the more electron-deficient C/F-rings. Despite this initial success, my attempts to optimize the CAN oxidation were met with difficulty due to bis-oxidation and formation of nitrated byproducts. A survey of other oxidants and conditions also proved fruitless.



Scheme 4.13 Biomimetic mono-oxidation of protected HMP-Y1.

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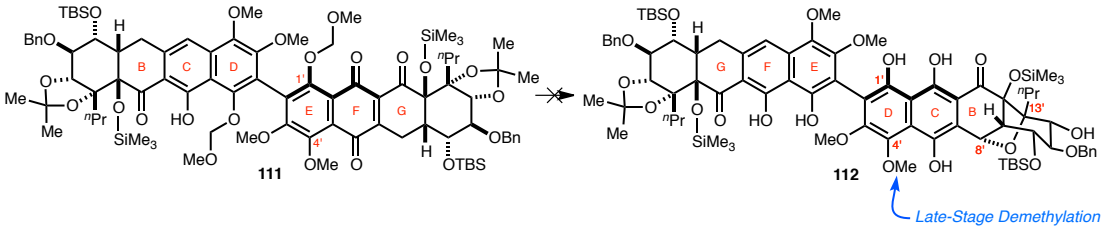
[107] (a) Preferential oxidation of the D-ring occurred in simpler BCD-ring model systems (i.e., **102**) and is suggested in the literature. (b) The ^{1}H NMR signal of the MOM groups of *ent*-**107a** and *ent*-**107b** are shifted over 0.6 ppm up-field relative to the corresponding monomer, suggesting that they are positioned over the naphthyl ring systems and subject to anisotropic magnetic field effects.

Nevertheless, with naphthazarin **111** in hand, I next investigated the desired biomimetic etherification reaction (Scheme 4.14). Unfortunately, exposure of **111** to the optimized conditions developed on the ABCD-model system led to no observable etherification but rather only to rapid MOM group cleavage, and upon further heating ultimately decomposition. A screen of various acids and conditions also proved unsuccessful, including those developed by Tatsuta et. al.[77] The resistance of **111** to undergo the desired etherification in contrast to the ABCD-ring system model quinone **85** was surprising (Scheme 4.8). Since the major difference between the two systems is the lability of the MOM groups of **111** relative to the methyl group of **85**, we postulated that a free phenol at C1' might disfavor either acetonide decomposition or formation of the necessary *o*-quinone methide intermediate. This prompted us to replace the MOM group with a more acid-stable protecting group.



Scheme 4.14 Failure of **111** to undergo a biomimetic etherification reaction.

Additionally, our current biomimetic strategy would inevitably require a late-stage demethylation of the C4'–OMe methyl group (Scheme 4.14). Ideally, one would remove the C4'–OMe methyl group as late in an eventual synthesis of hibarimicin B (**2**) as possible in order to protect the sensitive and stereochemically labile binaphthyl core (vide infra). However, the acidic conditions necessary to effect demethylation would be incompatible with the sensitive 2-deoxy- and 2,3-dideoxyglycosides of **2**. The aforementioned reasons prompted us to investigate our alternative strategy for the synthesis of hibarimicione (**6**) utilizing an unsymmetrical bidirectional annulation reaction.

Synthesis of Hibarimicinone

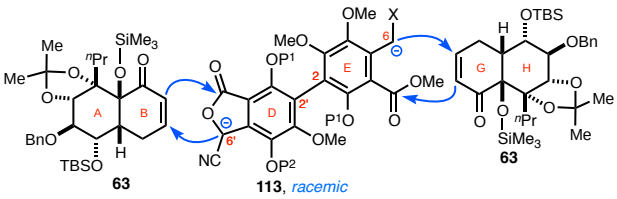


Figure 4.2 Proposed unsymmetrical bidirectional double annulation reaction.

In our alternative strategy, we envisaged that bidirectional double annulation reaction employing an unsymmetrical biaryl could be employed to construct the carbon framework of hibarimicinone (**6**) with the appropriate differential oxidation. More specifically, we anticipated that reaction of the lithiated cyanophthalide of **113** with AB/HG-enone **63** would directly construct the C-ring hydroquinone via a Kraus annulation, and reaction of the lithiated substituted *o*-toluate of **113** with a second equivalent of **63** would lead to the F-ring via a Michael–Claisen reaction sequence (Figure 4.2). The unsymmetrical fully substituted biaryl **113** presents unique synthetic challenges; cross-coupling technology to form sterically hindered biaryls from electron-rich aromatics is limited.[76d] In contrast, dimerization reactions to form hindered biaryls are robust and reliable (i.e., Scheme 4.11: **34** → **36**). Thus I imagined that a practical synthetic approach to **113** would necessitate the desymmetrization of **104** (Scheme 4.15). A strategy to mono-functionalize **104** involving radical bromination would inevitably result in an inefficient statistical mixture of benzylic bromides. However, I hypothesized that selective mono-deprotonation of **104** would be feasible since the initially formed carbanion would elevate the pK_a of the remaining *o*-toluate due to a field effect. Indeed, I discovered that selective mono-deprotonation of **104** at C6' could be achieved with 1.25 equivalents of LiTMP. The resultant anion **114** was then brominated with $(BrCF_2)_2$ to afford mono-benzylic bromide **115** in 82% yield. This single element of asymmetry was sufficient to introduce the remaining differential functionality. **115** was oxidized to aldehyde **116**,[108] which was then converted

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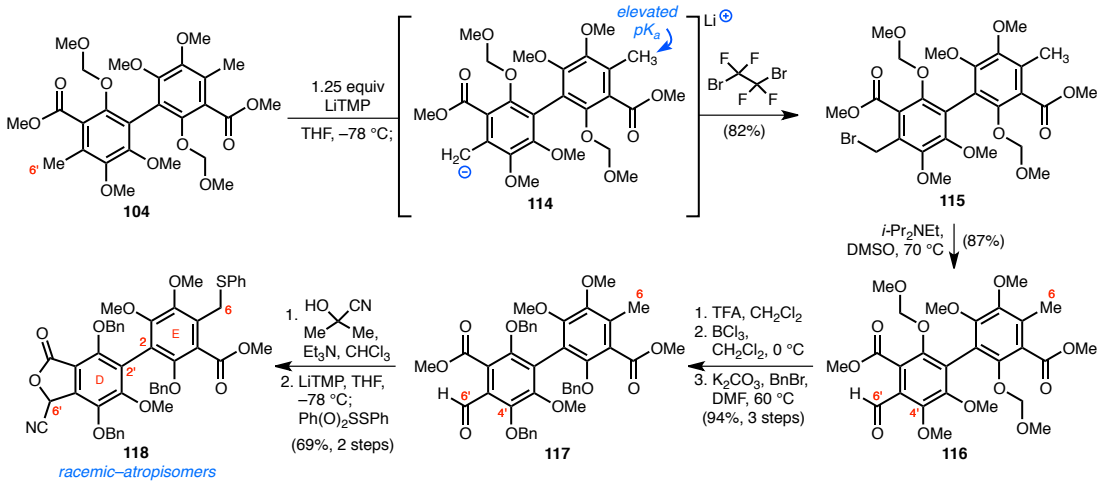
[108] Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114.

to tri-benzyl-protected biaryl **117** by (1) cleavage of the MOM groups, (2) chemoselective cleavage of the C4'–OMe methyl group with BCl_3, and (3) global reprotection with benzyl bromide. Treatment of **117** with hydrogen cyanide afforded a cyanophthalide intermediate.[109] Finally, double deprotonation of this intermediate with LiTMP, followed by short exposure[110] to *S*-phenyl benzenethiosulfonate, chemoselectively installed the phenyl sulfide moiety at C6 to provide biaryl **118**.[111] The observed chemoselectivity is a result of the much higher reactivity of the *o*-toluate anion relative to the cyanophthalide anion. This chemoselectivity could also be exploited to chemoselectively introduce a bromide or phenyl sulfoxide at C6 using $(Br_2CF)_2$ or methyl benzenesulfinate, respectively. It is worth mentioning that although only the synthesis of the ultimately successful biaryl **118** is depicted, the general strategy delineated in Scheme 4.15 was amenable to the synthesis of many biaryls that were used during the course of the project (Figure 4.3). For brevity, the synthesis of these biaryls as well as the related annulation and downstream studies will not be discussed.



Scheme 4.15 Synthesis of unsymmetrical biaryl **118** via a selective mono-deprotonation.

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[109] Sakulsombat, M.; Angelin, M.; Ramström, O. *Tetrahedron Lett*. **2010**, *51*, 75–78.

[110] Approximately ten seconds.

[111] Benzylic phenylsulfide substituted *o*-toluates were ultimately employed in our synthesis of hibarimicinone (**6**) due to the inability to make the corresponding C6-fluoride of **118**.

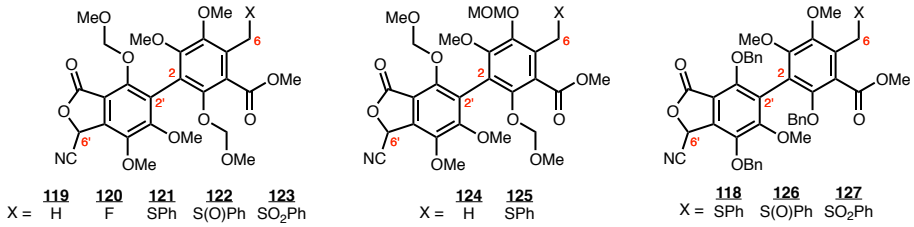

Figure 4.3 Biaryls synthesized and utilized in unsymmetrical bidirectional double annulation studies.

After extensive studies, I eventually found that the desired transformations could be achieved by treating a mixture of **118** and **63** with LiHMDS, followed by subsequent addition of KHMDS mid annulation sequence under rigorously oxygen-free conditions, to yield octacycle **128a** and **128b** as a ~1.3:1 mixture of atropisomers (Scheme 4.16).[112] The addition of KHMDS was crucial in facilitating the final intramolecular Claisen reaction to construct the F-ring.[113] At this stage, atropisomers **128a** and **128b** were separated and carried forward independently. The small coupling constant between the C6 and C7 hydrogen atoms of **128a** and **128b** suggest a *syn* relationship of the hydrogen atoms with respect to the ring system. This relative stereochemistry would preclude *syn*-elimination to aromatize the F-ring. In a related system, only one diastereomer of sulfoxide **126** underwent bidirectional annulation but failed to further undergo elimination to aromatize the F-ring, which occurred in situ during the corresponding monomer studies (Scheme 4.10).[114] Additionally, it is worth mentioning here that although C6-sulfone dihydronaphthalene EFGH-model systems underwent thermal elimination (sodium bicarbonate, xylenes, 140 °C), the presumed sulfone analogs of **128a** and **128b**

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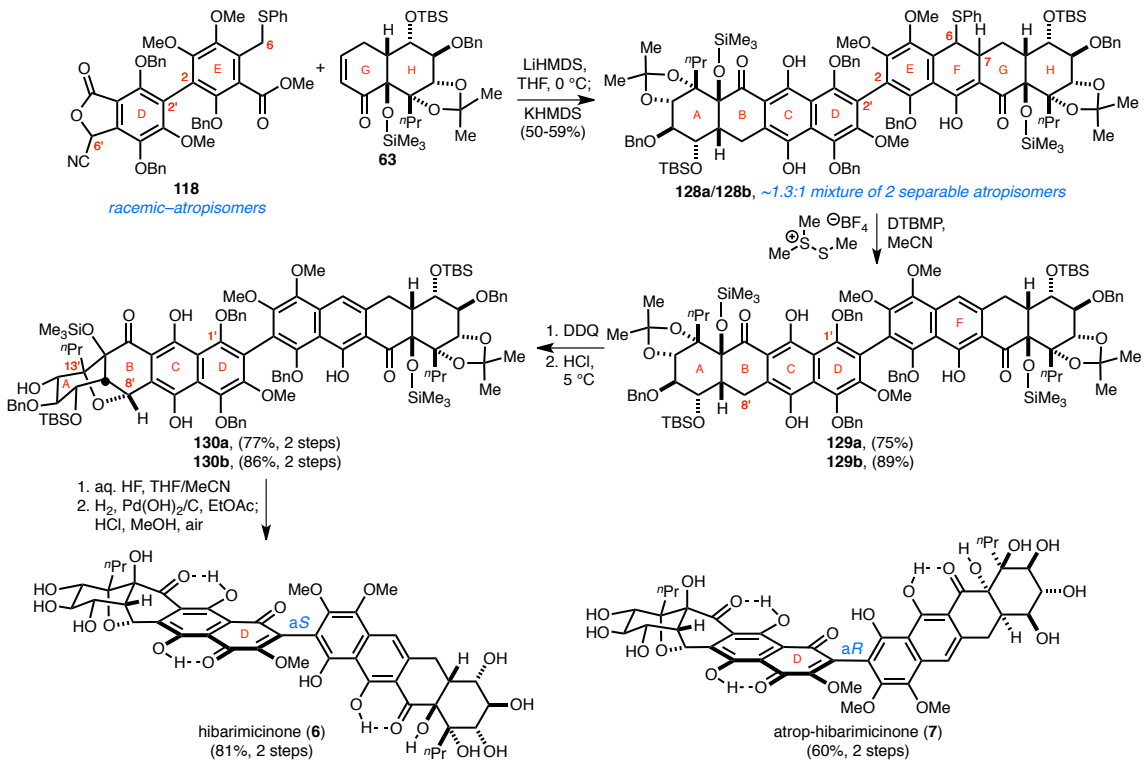
[112] (a) For brevity, each atropisomer is depicted as a single structure lacking stereochemistry about the C2–C2' bond. See Experimental Section for full details. (b) The regioisomer of the enolized 1,3-diketone was not determined and is arbitrarily depicted. (c) The C4'–OMe, MOM-protected biaryl **121** underwent cleaner bidirectional double annulation reaction (~80% yield), but the benzyl protecting groups were ultimately desired for aforementioned reasons.

[113] Kummer, D. A.; Li, D.; Dion, A.; Myers, A. G. *Chem. Sci.* **2011**, *2*, 1710–1718.

[114] Interestingly, while the Michael addition of the monomeric E-ring substituted *o*-toluate anions to *ent*-**63** were generally not diastereoselective, the corresponding bidirectional double annulations were completely diastereoselective.



Scheme 4.16 Completion of hibarimicinone (**6**) and atrop-hibarimicinone (**7**).

could not tolerate these conditions. In contrast, elimination of the C6-benzylic phenyl sulfide was successfully accomplished with DMTSF to yield binaphthalenes **129a** and **129b**.[115] These observations highlight the difficulty in achieving naphthol annulations in the context of complex molecule synthesis. To the best of our knowledge, this is the first example of a benzylic sulfide Michael–Claisen reaction sequence to generate naphthalenes and together with the benzylic fluoride Michael–Claisen reaction sequence offer two new alternative strategies to accomplish challenging naphthol annulations.

Oxidation of **129a** and **129b** by DDQ yielded the corresponding C-ring quinones. Gratifyingly, exposure of the respective quinones to anhydrous hydrochloric acid promoted the desired biomimetic etherification to yield nonacycles **130a** and **130b**. This successful etherification of

[115] Super stoichiometric amounts of silver(I) salts could also be employed, but the reactions were complicated by oxidation of the C-ring hydroquinone.

the benzyl protected naphthazarins, in contrast to MOM-protected **85**, confirmed our suspicion that the nature of the C1'-phenol has far-reaching electronic effects on this system. With the complete skeletons of **6** and **7** in hand, all that remained to complete the syntheses was global deprotection and oxidation of the D-ring. Deprotection of the acid-labile protecting groups was accomplished upon exposure to hydrofluoric acid. Finally, the benzyl groups were removed via hydrogenolysis and, after addition of acidic methanol, filtering, and exposure to air, hibarimicinone (**6**) and atrop-hibarimicinone (**7**) were formed. All of the spectroscopic data for **6** and **7** match those reported and thereby confirmed the structure of **7**.[73,77,116]

[116] Provided in a personal communication with Prof. H. Hori and Prof. Y. Igarashi.

Discovery of a pH-Dependent Rotational Barrier and Synthesis of HMP-P1

During the final benzyl deprotection of **130a** and **130b**, it was discovered that the addition of acidic methanol prior to aerobic oxidation was crucial to prevent isomerization between **6** and **7** as well as formation of HMP-P1 (**10**). Upon prolonged handling or standing at ambient temperatures in acidic methanol (1 M HCl), I observed minor interconversion between **6** and **7** as well as minimal

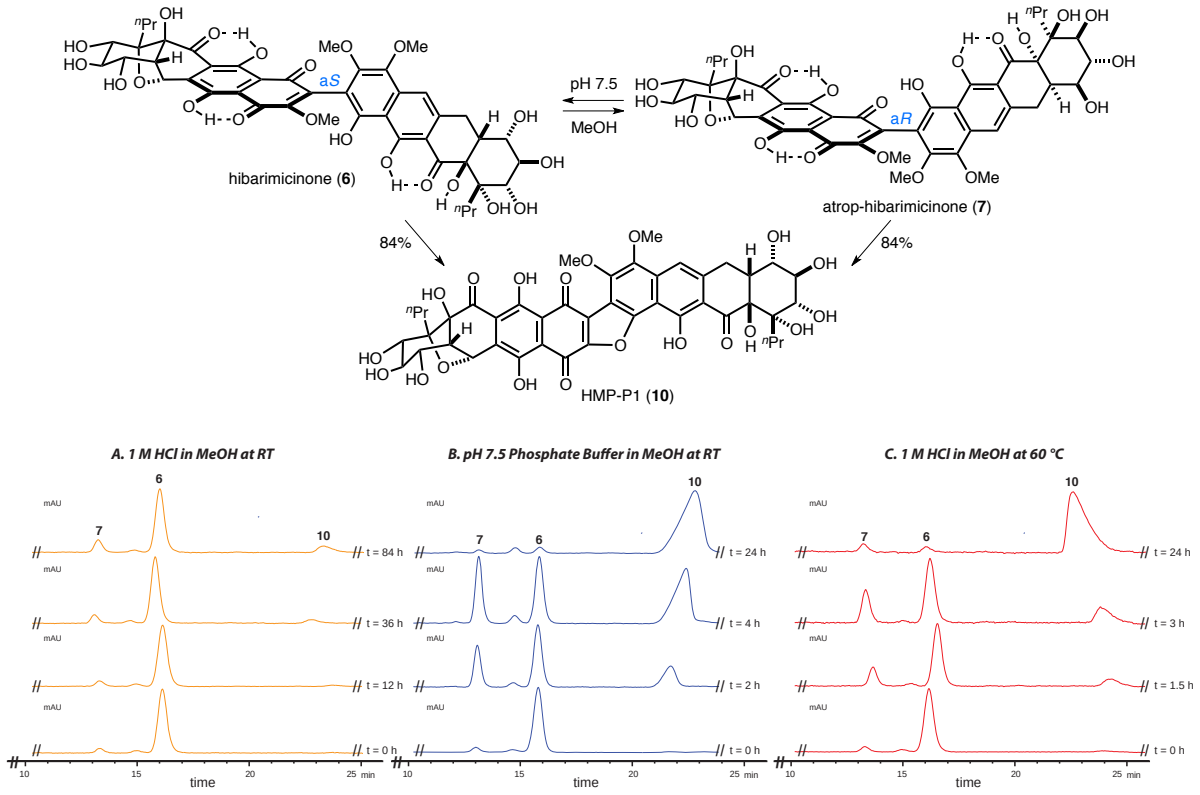


Figure 4.4 (**A**) Upon standing in acidic methanol (1 M HCl) at RT, hibarimicinone (**6**) and atrop-hibarimicinone (**7**) undergo minor interconversion and minimal conversion to HMP-P1 (**10**) (orange HPLC traces). (**B**) Exposure of **6** to pH 7.5 aqueous phosphate buffer at RT (blue HPLC traces) or (**C**) acidic methanol (1 M HCl) at 60 °C (red HPLC traces) resulted in isomerization to **7** and eventual formation of **10**.[117]

[117] See Figure S7 in Appendix C for HPLC time courses for **7**.

formation of **10** (Figure 4.4A). However, independent exposure of **6** and **7** to pH 7.5 buffered methanol led to the formation of **10** in 84% yield in both cases (Figure 4.4B). Monitoring these transformations by HPLC revealed that nearly complete isomerization about the C2–C2' bond (**6** ↔ **7**) had occurred within 4 hours, while formation of **10** was almost complete after 24 hours (Figure 4.4B). Together, these observations suggest that the rotational barriers about C2–C2' for **6** and **7** are pH-dependent.

These findings are particularly interesting due to prior observations that heating **6** in neutral methanol at 60 °C leads to nearly complete interconversion to **7** in 30 minutes, and ultimately complete cyclization to yield **10** after 90 minutes.[118] However, we found that heating either **6** or **7** to 60 °C in acidic methanol (1 M HCl) led to only partial interconversion between **6** and **7** and minor conversion to **10** after 90 minutes (Figure 4.4C). This suggests that the observed rapid rotation at 60 °C in neutral methanol has less to do with providing the necessary thermal energy to surpass the intrinsic activation barrier for rotation about C2–C2' in the uncharged forms of **6**/**7** (**131a**/**131b** in Figure 4.5), but rather enables access to the deprotonated form of **6** and **7** (**132a**/**132b** in Figure 4.5) via inter- or intramolecular proton transfer. Rapid interconversion between **132a** and **132b** can then follow through a transition state that is stabilized by π-electron overlap,[119] as depicted in cross-conjugated resonance structures **133a** and **133b**. Consequently, variables that affect the equilibrium between **131a** and **132a** as well as between **131b** and **132b,** will affect the rate of isomerization. The addition of acid to the media inhibits access to species **132a** and **132b** by driving the equilibrium toward **131a** and **131b**, and thus disfavors isomerization. In contrast, heat (60 °C) should promote equilibration between the protonation states and thus facilitate isomerization. Our discovery of the

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[118] Personal communication with Prof. H. Hori and Prof. Y. Igarashi.

[119] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994.

pH-dependent barrier demonstrates the delicate nature of the C2–C2' bond, which must be accommodated in an eventual synthesis of hibarimicin B (**2**).[120]

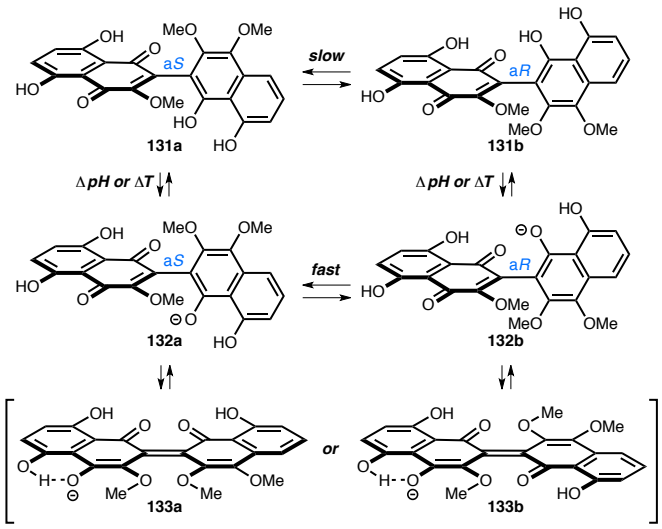

Figure 4.5 A proposed model to explain the pH-dependent rotational barrier about the C2–C2' bond of **6** and **7**. Only the CDEF-ring system is depicted for brevity.

[120] The carbohydrates of the hibarimicin natural products are cleaved with acidic methanol (1 M HCl, 30 °C). These conditions are similar to those employed during the benzyl deprotection and oxidation of **130a** and **130b**. However, milder acidic conditions (i.e., aq. pH 3.5 phosphate buffer) in methanol may potentially be substituted during the analogous deprotection and oxidation of **2** since these conditions are employed in the HPLC purification of **2** and hibarimicin related natural products. See ref. 73 for the conditions used for carbohydrate cleavage and purification of the hibarimicin natural products.

Conclusion

In conclusion, enantioselective syntheses of hibarimicinone (**6**) and atrop-hibarimicinone (**7**), and the first total syntheses of HMP-Y1 (**8**), atrop-HMP-Y1 (**110**), and HMP-P1 (**10**) have been accomplished. The complete carbon skeleton of each natural product was assembled via a convergent bidirectional annulation strategy. The use of a racemic biaryl in conjunction with the bidirectional annulation strategy enabled both atropisomers of the natural products to be separately constructed and fully characterized, thus providing the first reported full characterization of **7**, **8**, **110**, and **10**. Additionally, during the pursuit of this annulation strategy, we encountered numerous challenges when conducting naphthol annulation reactions. Consequently, we developed two valuable Michael–Claisen reaction sequences to construct complex naphthols that might find use as general methods. The mild conditions needed to dehydrohalogenate the benzylic fluoride intermediates are particularly noteworthy given the thermodynamic strength of C–F bonds.

The plausibility of our proposed biosynthesis was also validated by the demonstration that a desymmetrizing mono-oxidation of the C-ring could be conducted on protected HMP-Y1 derivatives. Over-oxidation to the bis-C/F-ring quinone was also observed, but natural products corresponding to such a double oxidation have not been isolated in nature or during mutagenesis studies. This perhaps suggests that an enzyme mediates this key biosynthetic transformation, but how HMP-Y1 (**8**) is only mono-oxidized remains unclear.

After the key bidirectional annulations, only three and five steps were needed to complete HMP-Y1 (**8**) and hibarimicinone (**6**), respectively. In the case of **6**, these steps include a biomimetic etherification to install the B-ring cyclic ether via an *o*-quinone methide intermediate. The success of this reaction required an acid-stable protecting group on the C1'-phenol due to subtle yet far-reaching electronic effects imparted by the naphthazarin-naphthalene system. The peculiarities and sensitivity of this system are also highlighted by our discovery of the pH-dependent rotational barrier about the

C2–C2' bond. These particular observations provide crucial information that will facilitate an eventual synthesis of hibarimicin B (**2**).

Lastly, the intermediate **130a** will be highly useful in an eventual total synthesis of **2**; it is suitably protected with orthogonal protecting groups to allow for the sequential installation of the 2-deoxy- and 2,3-dideoxyglycosides prior to deprotection of the sensitive binaphthyl core of the molecule. B. Milgram is already well advanced in this ultimate endeavor and hopefully a synthesis of **2** will soon be accomplished.

Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried glassware under a positive pressure of argon unless otherwise noted. Where necessary (so noted), reactions were performed in Schlenk tubes fitted with a PTFE stopcock or pressure tubes fitted with a PTFE bushing. Flash column chromatography was performed as described by Still et al. employing silica gel 60 (40-63 μm, Whatman).[121] Preparatory thin-layer chromatography (PTLC) was performed using 0.25 or 0.50 mm silica gel 60 F_{254} plates purchased from EMD Chemicals. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F_{254} plates or 0.25 mm silica gel RP-18 F_{254s} plates (so noted) purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to an acidic solution of *p*-anisaldehyde (anis) or an aqueous solution of ceric ammonium molybdate (CAM) followed by heating on a hot plate. HPLC purification was performed on an Agilent 1100 series HPLC. Hibarimicinone (**6**) and atrop-hibarimicinone (**7**) isomerization studies were performed on the same instrument. HMP-Y1 (**8**) and atrop-HMP-Y1 (**110**) isomerization studies were conducted on an Agilent 1200 series 6120 quadrupole LC/MS.

Materials. Commercial reagents and solvents were used as received with the following exceptions: THF, diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), HMDS, toluene (PhMe), benzene (PhH), and DMF were degassed with argon and passed through a solvent purification system (designed by J.C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al. [122] Triethylamine (Et_3N), diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, pyridine (Py), and chlorotrimethylsilane (TMSCl) were distilled over calcium hydride before use. *N*,*N*,*N'*,*N'*-Tetramethylethylenediamine (TMEDA) was distilled over potassium

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[121] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[122] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

hydroxide immediately before use. TMSOTf was distilled before use. Methanol used for the CD and UV–vis measurements was HPLC grade purchased from EMD. The Celite used was Celite® 545, purchased from J.T. Baker. Where necessary (so noted), commercial *m*-CPBA (technical grade, 77% purity) was purified to >95% purity by the procedure described by Bartolini and coworkers.[123] The molarities of *n*-butyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of three determinations). The molarity of *n*-propylmagnesium chloride solution was determined by titration with iodine according to the protocol of Knochel and Krasovsky (average of three determinations).[124] Anhydrous cerium(III) chloride was obtained by drying cerium(III) chloride heptahydrate under reduced pressure according to the procedure of Dimitrov and coworkers.[125] Where necessary (so noted), solutions were deoxygenated by alternating freeze (liquid nitrogen)/evacuation/thaw cycles (FPT, five iterations).

Instrumentation. ^{1}H NMR spectra were recorded with a Varian INOVA-600, Varian INOVA-500, or Varian Mercury 400 spectrometer, are reported in parts per million (δ), and are calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 7.26 ($CHCl_3$), CD_2Cl_2: δ 5.32 ($CDHCl_2$), CD_3OD: δ 3.31 (CD_2HOD), C_6D_6: δ 7.16 (C_6D_5H)). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. ^{13}C NMR spectra were recorded with a Varian INOVA-500 or Varian Mercury 400 spectrometer, are reported in parts per million (δ) and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.00, CD_2Cl_2: δ 54.00, CD_3OD: δ 49.15, C_6D_6: δ 128.39, DMSO-d_6: 39.51). Infrared (IR) data were recorded on a Varian 1000 Scimitar

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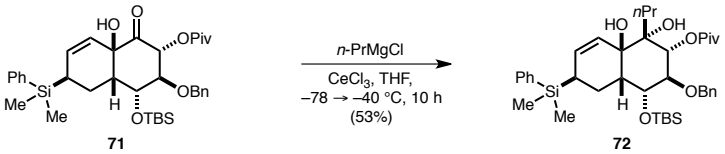
[123] Bortolini, O.; Campestrini, S.; Di Fuiria, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093–5095.

[124] Krasovsky, A.; Knochel, P. *Synthesis* **2006**, *5*, 0890–0891.

[125] Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787–6790.

FT-IR spectrophotometer, were referenced to a polystyrene standard, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy experiments on an Agilent 6210 TOF LC/MS. Optical rotations were measured on a Jasco P-2000 digital polarimeter with a sodium lamp (average of at least four measurements for each sample). Circular dichroism (CD) spectra were collected on a Jasco J-710 spectropolarimeter equipped with a temperature controller (at 23 ± 0.1 °C) using the following standard measurement parameters: 0.5 nm step resolution, 50 nm/sec speed, 4 accumulations, 1 sec response, 1 nm bandwidth, 1.0 cm path length. All spectra were converted to a uniform scale of molar ellipticity after background subtraction. Curves shown are smoothed with standard parameters. The UV-vis absorption spectra were recorded on a Hitachi UV spectrophotometer, Model U-3010 at ambient temperature (23 ± 2 °C) using a quartz 1-cm cuvette (3 mL) and the following standard measurement parameters: 1.0 nm step resolution, 10 nm/sec speed, 1 accumulation, 1 sec response, 1 nm bandwidth. Background was corrected with respect to a reference cuvette containing the same methanol as the sample cuvette. Curves shown are smoothed with standard parameters.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with **S1**).*



Diol 72: A 50-mL Schlenk flask was charged with anhydrous cerium(III) chloride (0.290 g, 1.18 mmol, 15.0 equiv) and heated to 150 °C under reduced pressure (~0.1 Torr). After 2.5 h, the flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (8 mL) was introduced via syringe. The resultant stirred heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 10 h, the reaction mixture was cooled to –78 °C before a solution of *n*-propylmagnesium chloride in Et_2O (1.72 M, 0.550 mL, 0.942 mmol, 12.0 equiv) was added dropwise via syringe. After 3 h, a solution of ketone **71**[126] (50 mg, 0.079 mmol, 1.0 equiv) in THF (1 mL) was added dropwise via syringe to the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 500 µL). After 3 h, the stirred reaction mixture was slowly allowed to warm to –40 °C over 10 h, after which saturated aqueous NH_4Cl solution (5 mL) was added. The resultant mixture was allowed to warm to ambient temperature before water (10 mL) and Et_2O (20 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% → 17% → 33% EtOAc in hexanes) to afford diol **72** (28 mg, 53%). **^{1}H NMR** (600 MHz, C_6D_6) δ: 7.51–7.47 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.28–7.23 (m, 3H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 5.89 (d, *J* = 10.0 Hz, 1H), 5.73 (dd, *J* = 3.7, 10.1 Hz, 1H), 5.23 (dd, *J* = 2.6, 10.3 Hz, 1H), 4.98 (d, *J* = 12.3 Hz, 1H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.44 (dd, *J* = 6.2, 10.0 Hz, 1H), 4.07 (t, *J* = 9.8 Hz, 1H), 2.63 (dt, *J* = 8.5, 14.2 Hz, 1H), 2.34 (dd, *J* = 4.5, 13.9 Hz, 1H), 1.91–1.83 (m, 2H), 1.67–1.51 (m, 4H), 1.41 (br. s., 1H), 1.15 (s, 9H), 0.93 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H),

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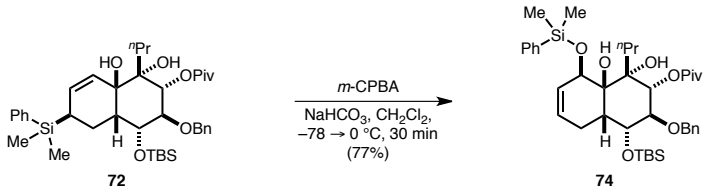
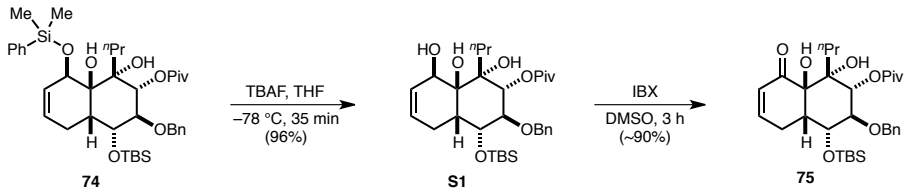
[126] For brevity, see Milgram, B. C.; Liau, B. B.; Shair, M. D. *Org. Lett.* **2011**, *13*, 6436–6439 for the preparation of **71**.

0.32 (s, 3H), 0.33 (s, 3H), –0.02 (s, 3H), –0.06 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 177.4, 140.1, 138.4, 135.0, 134.6, 129.9, 128.7, 127.3, 127.1, 126.5, 79.7, 79.1, 75.9, 75.6, 75.2, 72.8, 48.9, 39.5, 39.2, 30.6, 27.8, 26.8, 26.6, 20.3, 19.1, 18.5, 15.9, –3.2, –3.5, –4.1, –4.1. **HRMS** (ESI) (*m/z*) calc'd for $C_{39}H_{60}NaO_6Si_2$ $[M+Na]^+$: 703.3821, found 703.3815. **TLC** (15% EtOAc in hexanes), R_f: 0.32 (CAM).



Allylic silylether 74: A solution of *m*-CPBA (77 wt. %, 18.5 mg, 0.0830 mmol, 2.01 equiv) in CH_2Cl_2 (500 µL) was added dropwise via syringe to a stirred solution of diol **72** (28 mg, 0.041 mmol, 1.0 equiv) and $NaHCO_3$ (5.2 mg, 0.062 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) at –78 °C, which was subsequently allowed to warm to 0 °C. After 30 min, saturated aqueous Na_2SO_3 solution (1 mL) was added via syringe to the stirred reaction mixture, which was then allowed to warm to ambient temperature. Saturated aqueous Na_2SO_3 solution (5 mL) and Et_2O (5 mL) were then added and the layers were separated. The aqueous layer was extracted with Et_2O (5 mL) and EtOAc (2 × 5 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford allylic silylether **74** (22.0 mg, 77%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 1.6, 7.8 Hz, 2H), 7.45–7.38 (m, 3H), 7.30–7.23 (m, 4H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.00 (ddd, *J* = 2.1, 4.7, 9.7 Hz, 1H), 5.71–5.66 (m, 1H), 5.44 (d, *J* = 9.7 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.39 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.19 (d, *J* = 4.7 Hz, 1H), 3.78 (t, *J* = 9.5 Hz, 1H), 3.16 (s, 1H), 2.44 (dd, *J* = 12.0, 18.7 Hz, 1H), 2.32 (td, *J* = 5.3, 19.0 Hz, 1H), 2.16 (td, *J* = 6.4, 12.3 Hz, 1H), 1.74 (br. s, 1 H), 1.48–1.35 (m, 1H), 1.34–1.23 (m, 1H), 1.23–1.13 (m, 1H), 1.07 (s, 9H), 0.88 (s, 9H), 0.71 (t, *J* = 7.3 Hz, 3H), 0.50 (s, 3H), 0.46 (s, 3H), 0.05 (s, 3H), –0.06 (s, 3H). **^{13}C NMR** (126MHz, $CDCl_3$) δ: 176.7, 139.1, 136.7, 133.5, 133.0, 130.1, 128.1, 127.9, 126.6, 126.5, 126.2, 79.4, 78.8, 76.5, 74.6, 74.2, 72.1, 66.9, 42.9, 38.9, 38.1, 27.2, 26.3, 26.0, 18.3, 18.0, 14.9, –0.8, –0.9, –4.7, –4.7. **FTIR** (thin film) cm^{-1}: 3518, 2925, 1736, 1463, 1256, 1119, 836. **HRMS** (ESI) (*m/z*) calc'd for $C_{39}H_{60}NaO_7Si_2$ $[M+Na]^+$: 719.3770, found 719.3735. **TLC** (25% EtOAc in hexanes), R_f: 0.75 (CAM).



Enone 75: A solution of TBAF in THF (1.0 M, 8.0 µL, 8.0 µmol, 1.1 equiv) was added dropwise via syringe to a stirred solution of **74** (5.0 mg, 7.2 µmol, 1.0 equiv) in THF (400 µL) at –78 °C. After 35 min, saturated aqueous NH_4Cl solution (500 µL) was added to the stirred reaction mixture, which was allowed to warm to ambient temperature. Saturated aqueous NH_4Cl solution (5 mL), Et_2O (5 mL), and EtOAc (5 mL) were then added to the mixture and the layers were separated. The organic layer was washed water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10% → 30% EtOAc in hexanes) to afford the alcohol **S1** (3.9 mg, 96%).

IBX (5.8 mg, 21 µmol, 3.0 equiv) was added to a stirred solution of **S1** (3.9 mg, 6.9 µmol, 1.0 equiv) in DMSO (400 µL). After 3 h, a 1:1 mixture of saturated aqueous Na_2SO_3 solution and saturated aqueous $NaHCO_3$ solution (5 mL), Et_2O (5 mL), and EtOAc (5 mL) were added to the reaction mixture. The layers were separated, and the organic layer was washed saturated aqueous $NaHCO_3$ solution (2 × 10 mL), water (3 × 10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparatory thin-layer chromatography (silica gel, 0.25 mm, eluent: 20% EtOAc in hexanes) to afford enone **75**[127] (~3.5 mg, ~90%). **^{1}H NMR** (600MHz, C_6D_6) δ: 7.42 (d, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.06 (dd, *J* = 7.3, 9.4 Hz, 1H), 6.59–6.53 (m, 1H), 6.12 (dd, *J* = 2.3, 10.0 Hz, 1H), 5.86 (d, *J* = 9.7 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.49 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.13 (s, 1H), 3.95 (t, *J* = 9.7 Hz, 1H), 2.97– 2.87 (m, 1H), 2.58–2.45 (m, 2H), 1.47–1.28 (m, 4H), 1.03 (s, 9H), 0.93 (s, 9H), 0.74 (t, *J* = 7.2 Hz, 3H), –0.05 (s, 3H), –0.08 (s, 3H). **HRMS** (ESI) (*m/z*) calc'd for $C_{29}H_{44}NaO_6Si$ $[M+Na]^+$: 539.2799, found 539.2795. **TLC** (33% EtOAc in hexanes), R_f: 0.68 (UV, anis).

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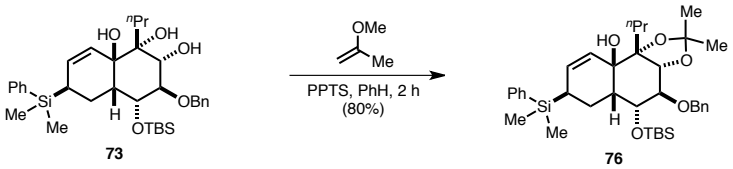
[127] Enone **75** was only characterized by HRMS and ^{1}H NMR analysis.



Acetonide 76: Pyridinium *p*-toluenesulfonate (75.4 mg, 0.300 mmol, 0.100 equiv) was added in a single portion to a stirred solution of triol **73**[128] (92 mg, 0.15 mmol, 1.0 equiv) and 2-methoxypropene (294 μL, 3.08 mmol, 20.0 equiv) in benzene (3 mL). After 2 h, saturated aqueous $NaHCO_3$ solution (5 mL) and Et_2O (5 mL) were added to the stirred reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 6% EtOAc in hexanes) to afford acetonide **76** (78 mg, 80%) as a colorless flocculent solid. **^{1}H NMR** (500 MHz, C_6D_6) δ: 7.54–7.50 (m, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.25–7.16 (m, 5H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.08 (dd, *J* = 1.6, 10.3 Hz, 1H), 5.85 (dd, *J* = 1.4, 10.3 Hz, 1H), 4.97 (d, *J* = 11.9 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.12 (dd, *J* = 8.2, 11.0 Hz, 1H), 4.10 (d, *J* = 6.2 Hz, 1H), 4.00 (dd, *J* = 6.2, 11.2 Hz, 1H), 2.38–2.27 (m, 3H), 2.06–1.96 (m, 2H), 1.79 (dtdd, *J* = 5.2, 7.2, 12.6, 19.9 Hz, 1H), 1.70–1.58 (m, 1H), 1.55–1.47 (m, 4H), 1.30 (s, 3H), 0.98 (s, 9H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.32 (s, 3H), 0.32 (s, 3H), 0.15 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 139.9, 138.1, 134.7, 131.8, 130.7, 129.8, 128.9, 128.6, 128.5, 127.8, 109.3, 87.8, 87.2, 81.0, 73.3, 72.9, 70.1, 43.3, 40.2, 28.0, 27.3, 26.8, 24.5, 21.1, 19.1, 18.9, 15.8, –3.7, –3.8, –4.1, –4.6. **FTIR** (thin film) cm^{-1}: 3467, 2958, 2930, 2860, 1639, 1461, 1380, 1252, 1208, 1114, 1032, 837, 774, 734, 699. **HRMS** (ESI) (*m/z*) calc'd for $C_{37}H_{56}O_5Si_2Na$ $[M+Na]^+$: 659.3559, found 659.3576. **TLC** (15% EtOAc in hexanes), R_f: 0.63 (UV, CAM, anis).

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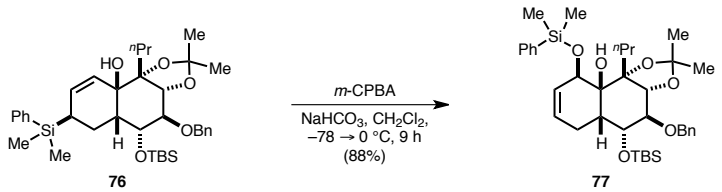
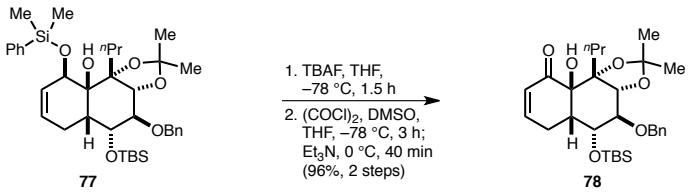
[128] For brevity, see Milgram, B. C.; Liau, B. B.; Shair, M. D. *Org. Lett.* **2011**, *13*, 6436–6439 for the preparation of **73**.



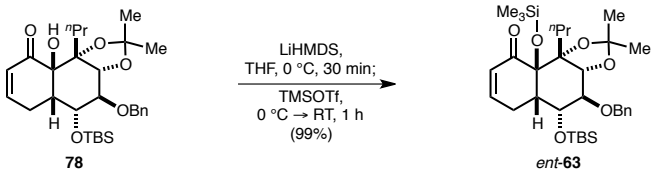
Allylic silylether 77: A solution of *m*-CPBA (77 wt. %, 350 mg, 1.56 mmol, 2.00 equiv) in CH_2Cl_2 (5 mL) was added dropwise via syringe to a stirred solution of acetonide **76** (497 mg, 0.780 mmol, 1.00 equiv) and $NaHCO_3$ (200 mg, 2.34 mmol, 3.00 equiv) in CH_2Cl_2 (25 mL) at –78 °C, which was subsequently allowed to warm to –5 °C over 30 min. After an additional 8.5 h, saturated aqueous Na_2SO_3 solution (20 mL) was added via syringe to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. Et_2O (20 mL) was then added to the resultant mixture and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with saturated aqueous Na_2SO_3 solution (50 mL), saturated aqueous $NaHCO_3$ solution (2 × 50 mL), water (50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford allylic silylether **77** (448 mg, 88%) as a colorless flocculent solid. **^{1}H NMR** (500 MHz, C_6D_6) δ: 7.54–7.50 (m, 4H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.20–7.16 (m, 3H), 7.11 (t, *J* = 7.6 Hz, 1H), 5.85–5.76 (m, 2H), 5.11 (d, *J* = 11.7 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.72 (dd, *J* = 3.9, 9.3 Hz, 1H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.39 (d, *J* = 5.1 Hz, 1H), 3.94 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.89 (s, 1H), 2.61–2.52 (m, 1H), 2.44–2.35 (m, 2H), 2.29 (ddd, *J* = 5.6, 12.0, 14.2 Hz, 1H), 1.63–1.43 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H), 1.01 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.32 (s, 3H), 0.30 (s, 3H), 0.21 (s, 3H), 0.16 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ: 139.7, 137.4, 133.9, 130.3, 130.2, 128.6, 128.4, 128.3, 128.2, 127.5, 109.4, 88.9, 87.0, 83.0, 73.8, 73.1, 71.2, 68.1, 44.0, 41.3, 29.0, 28.5, 26.2, 25.5, 18.7, 18.4, 15.4, –0.7, –0.7, –4.0, –4.6. **FTIR** (thin film) cm^{-1}: 3490, 2956, 2929, 2894, 2856, 1456, 1429, 1378, 1254, 1234, 1118, 1038, 835, 787, 736, 698. **HRMS** (ESI) (*m/z*) calc'd for $C_{37}H_{56}O_6Si_2Na$ $[M+Na]^+$: 675.3508, found 675.3505. **TLC** (15% EtOAc in hexanes), R_f: 0.65 (UV, CAM, anis).



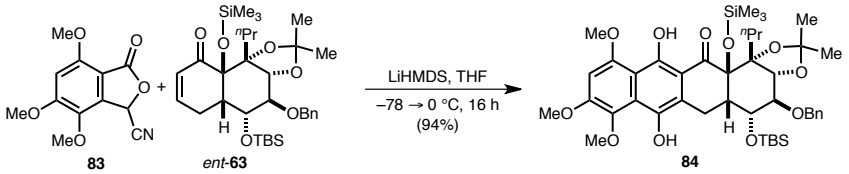
Enone 78: A solution of TBAF in THF (1.0 M, 1.0 mL, 1.0 mmol, 1.5 equiv) was added dropwise via syringe to a stirred solution of **77** (448 mg, 0.686 mmol, 1.00 equiv) in THF (7 mL) at –78 °C. After 1.5 h, saturated aqueous NH_4Cl solution (5 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. Saturated aqueous NH_4Cl solution (10 mL) and Et_2O (20 mL) were then added to the resultant mixture and the layers were separated. The aqueous later was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed water (40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% EtOAc in hexanes) to afford the corresponding allylic alcohol, which was carried forward to the next reaction.

Oxalyl chloride (465 µL, 5.49 mmol, 8.00 equiv) was added dropwise via syringe to a stirred solution of DMSO (780 µL, 11.0 mmol, 16.0 equiv) in CH_2Cl_2 (6 mL) at –78 °C. After 1 h, a solution of the allylic alcohol in CH_2Cl_2 (3 mL) at –78 °C was added dropwise via a dry-ice wrapped cannula to the stirred reaction mixture at –78 °C. The transfer was completed with three additional portions of CH_2Cl_2 (3 × 1 mL). After 3 h, Et_3N (3.00 mL, 22.0 mmol, 32.0 equiv) was added down the flask wall into the stirred reaction mixture at –78 °C, which after 5 min was allowed to warm to 0 °C. After an additional 40 min at 0 °C, saturated aqueous NH_4Cl solution (20 mL) and Et_2O (25 mL) were added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL) and EtOAc (2 × 15 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl solution (50 mL), water (3 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent:

gradient, 5% → 6% EtOAc in hexanes) to afford enone **78** (340 mg, 96%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.29–7.24 (m, *J* = 7.4, 7.4 Hz, 1H), 6.97 (ddd, *J* = 2.2, 5.4, 9.9 Hz, 1H), 6.20 (dd, *J* = 2.1, 10.1 Hz, 1H), 4.91 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.25 (s, 1H), 4.15 (dd, *J* = 4.9, 9.5 Hz, 1H), 4.06 (d, *J* = 5.9 Hz, 1H), 3.75 (dd, *J* = 5.9, 9.5 Hz, 1H), 2.68 (tdd, *J* = 2.8, 11.2, 20.0 Hz, 1H), 2.57 (td, *J* = 5.6, 20.0 Hz, 1H), 2.32 (td, *J* = 5.6, 11.0 Hz, 1H), 2.04 (ddd, *J* = 7.8, 10.0, 14.9 Hz, 1H), 1.59–1.51 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.24–1.15 (m, 2H), 0.91–0.86 (m, 9H), 0.79 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 201.0, 151.3, 138.7, 128.1, 127.9, 127.6, 127.3, 110.1, 88.0, 85.9, 81.7, 76.0, 73.2, 70.1, 47.9, 37.8, 29.0, 28.4, 26.2, 25.9, 18.1, 16.1, 14.6, –4.5, –4.9. **FTIR** (thin film) cm^{-1}: 3462, 2955, 2930, 2891, 2858, 1677, 1473, 1380, 1254, 1231, 1110, 1089, 1030, 853,837, 777, 735, 697. **HRMS** (ESI) (*m/z*) calc'd for $C_{29}H_{44}O_6SiNa$ $[M+Na]^+$: 539.2799, found 539.2796. **TLC** (15% EtOAc in hexanes), R_f: 0.55 (UV, CAM).



***ent*-AB/HG-Enone *ent*-63:** A 25-mL round-bottom flask was charged with enone **78** (340 mg, 0.658 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (13 mL) was introduced, and the resultant solution cooled to 0 °C. A freshly prepared solution of LiHMDS in THF/hexanes (1.00 M, 1.32 mL, 1.32 mmol, 2.00 equiv) was added dropwise via syringe to the stirred reaction mixture. After 30 min, a solution of TMSOTf (357 µL, 1.97 mmol, 3.00 equiv) in toluene (1.64 mL) was added dropwise via syringe to the stirred reaction mixture at 0 °C. After 30 min, the reaction was allowed to warm to ambient temperature. After an additional 30 min, saturated aqueous NH_4Cl solution (10 mL) and Et_2O (20 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with Et_2O (10 mL) and EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel, eluent: 4% EtOAc in hexanes) to afford *ent*-AB/HG-enone *ent*-**63** (382 mg, 99%) as a colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29–7.24 (m, 1H), 6.88 (ddd, *J* = 2.2, 4.9, 9.8 Hz, 1H), 6.11 (dd, *J* = 2.4, 10.0 Hz, 1H), 4.91 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.15 (dd, *J* = 5.0, 9.4 Hz, 1H), 4.07 (d, *J* = 5.6 Hz, 1H), 3.74 (dd, *J* = 5.7, 9.4 Hz, 1H), 2.65 (tdd, *J* = 2.7, 11.0, 19.8 Hz, 1H), 2.57 (td, *J* = 5.9, 19.5 Hz, 1H), 2.34 (td, *J* = 5.6, 10.9 Hz, 1H), 1.91 (ddd, *J* = 5.4, 12.2, 14.6 Hz, 1H), 1.76–1.65 (m, 1H), 1.41–1.29 (m, 7H), 1.24–1.14 (m, 1H), 0.90 (s, 9H), 0.80 (t, *J* = 7.3 Hz, 3H), 0.16 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 199.2, 149.1, 138.7, 129.4, 128.0, 127.9, 127.3, 109.9, 87.1, 86.2, 81.9, 81.1, 73.2, 70.4, 49.1, 38.3, 28.8, 28.4, 26.7, 25.9, 18.0, 16.7, 14.5, 2.2, –4.5, –4.7. **FTIR** (thin film) cm^{-1}: 2952, 1689, 1250, 1123, 1090, 840. **HRMS** (ESI) (*m/z*) calc'd for $C_{32}H_{53}O_6Si_2$ $[M+H]^+$: 589.3375, found 589.3367. **TLC** (15% EtOAc in hexanes), R_f: 0.69 (UV, CAM).



ABCD-tetracycle (–)-84: A 10-mL Schlenk tube was charged with cyanophthalide **83**[129] (33.0 mg, 132 μmol, 1.50 equiv) and *ent*-AB/HG-enone *ent*-**63** (52.0 mg, 88.3 μmol, 1.00 equiv), which were then azeotropically dried with five portions of benzene. THF (2 mL) was then introduced, and the resultant solution was deoxygenated via FPT and then cooled to –78 °C. A solution of freshly prepared deoxygenated LiHMDS in THF/hexanes (1.00 M, 400 μL, 400 μmol, 4.53 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 2 h. After 14 h, a saturated aqueous NH_4Cl solution (3 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (10 mL), EtOAc (10 mL), and saturated aqueous NH_4Cl solution (10 mL), and the layers were separated. The organic layers were then washed with saturated aqueous NH_4Cl solution (20 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 11% → 25% EtOAc in hexanes) to afford ABCD-tetracycle (–)-**84** (67.0 mg, 94%) as a yellow film. **^{1}H NMR** (600 MHz, CD_2Cl_2) δ: 14.36 (br. s., 1H), 9.61 (br. s., 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 6.9 Hz, 1H), 6.60 (br. s., 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.26 (dd, *J* = 4.7, 9.1 Hz, 1H), 4.19 (d, *J* = 4.4 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.92 (dd, *J* = 4.4, 9.1 Hz, 1H), 3.41–3.29 (m, 1H), 3.08–2.93 (m, 1H), 2.46–2.35 (m, 1H), 2.00–1.93 (m, 1H), 1.91–1.84 (m, 1H), 1.56–1.46 (m, 1H), 1.36–1.29 (m, 1H), 1.25 (s, 3H), 1.18 (s, 3H), 0.93 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 6H), 0.18 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 203.2, 159.4, 159.0, 152.8, 140.2, 139.6, 136.1, 128.6, 128.4, 127.8, 124.6, 120.2, 111.7, 110.8, 110.0, 95.3, 87.6, 87.0, 83.5, 81.7, 73.5, 71.8, 62.8, 57.1, 56.9, 48.0, 40.3, 28.4, 27.8, 26.3, 21.5, 18.6, 17.9, 15.2, 2.4, –

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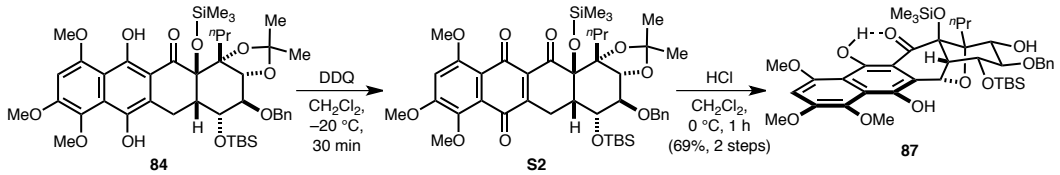
[129] Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921–9926.

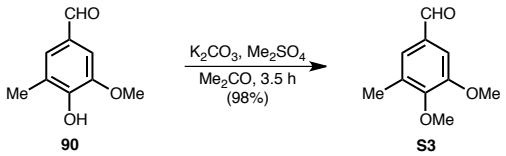
4.1, –4.2. **FTIR** (thin film) cm^{-1}: 3329, 2945, 1603, 1394, 1091, 1034, 846. **HRMS** (ESI): calc'd for $C_{43}H_{63}O_{11}Si_2$ $[M+H]^+$: 811.3903, found 811.3852. $\mathbf{[\alpha]_D^{22}}$: –39.5 (*c* = 1.0, $CHCl_3$). **TLC** (33% EtOAc in hexanes), R_f: 0.50 (UV, CAM).



Pentacyclic ether (+)-**87:** DDQ (5.8 mg, 26 μmol, 2.0 equiv) was added in one portion to a stirred solution of **84** (10.6 mg, 13.1 μmol, 1.00 equiv) in CH_2Cl_2 (1 mL) at –20 °C. After 30 min, a 1:1 mixture of 1% (w/v) aqueous $NaHSO_3$ solution (2.5 mL) and saturated aqueous $NaHCO_3$ solution (2.5 mL) was added to the reaction mixture. The mixture was diluted with Et_2O (10 mL) and EtOAc (10 mL), and the layers were separated. The combined organic layers were washed with a 1:1 mixture of a 1% (w/v) aqueous $NaHSO_3$ solution and saturated aqueous $NaHCO_3$ solution (2 × 10 mL), saturated $NaHCO_3$ aqueous solution (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude naphthazarin **S2**, which was used immediately without further purification.

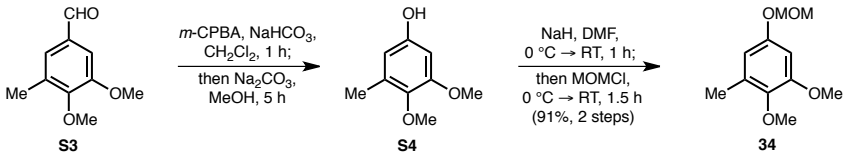
A 50-mL round-bottom flask was charged with crude **S2** and was azeotropically dried with four portions of benzene. CH_2Cl_2 (11 mL) was then introduced, and the resultant solution was cooled to 0 °C. A solution of anhydrous HCl in Et_2O (2.0 M, 160 μL, 330 μmol, 25 equiv) was added dropwise via syringe to the stirred solution. After 4 h, saturated aqueous $NaHCO_3$ solution (10 mL) was added to the stirred reaction mixture. The mixture was diluted with EtOAc (25 mL) and the layers were separated. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by preparatory thin-layer chromatography (eluent: 33% EtOAc in hexanes) to afford pentacyclic ether (+)-**87** (6.9 mg, 69% over two steps) as a yellow-green film. **^{1}H NMR** (600 MHz, CD_2Cl_2) δ: 14.35 (s, 1H), 9.60 (s, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.30–7.26 (m, 1H), 6.60 (s, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.25 (dd, *J* = 4.7, 9.0 Hz, 1H), 4.19 (d, *J* = 4.4 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.92 (dd, *J* = 4.5, 8.9 Hz, 1H), 3.35 (dd, *J* = 6.1, 17.9 Hz, 1H), 3.01 (dd, *J* = 13.4, 18.1 Hz,

1H), 2.40 (td, *J* = 5.6, 12.9 Hz, 1H), 1.96 (ddd, *J* = 4.1, 12.5, 14.3 Hz, 1H), 1.87 (ddd, *J* = 5.1, 12.0, 14.3 Hz, 1H), 1.56–1.46 (m, 1H), 1.36–1.28 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 0.92 (s, 9H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.18 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 202.5, 160.2, 159.1, 153.6, 140.1, 139.3, 137.3, 128.8, 128.2, 127.9, 125.0, 122.2, 111.6, 108.3, 96.5, 88.1, 87.5, 85.1, 75.5, 74.5, 72.5, 69.9, 62.9, 58.3, 57.2, 56.9, 35.7, 26.1, 18.3, 16.8, 15.1, 2.1, –4.1, –4.1. **FTIR** (thin film) cm^{-1}: 3315, 2952, 1623, 1597, 1394, 1252, 1094, 887, 839. **HRMS** (ESI): calc'd for $C_{40}H_{57}O_{11}Si_2$ $[M+H]^+$: 769.3434, found 769.3425. **$[\alpha]_D^{23}$**: 22.7 (*c* = 0.50, $CHCl_3$). **TLC** (33% EtOAc in hexanes), R_f: 0.36 (UV, CAM).



5-Methylveratraldehyde (S3): Dimethylsulfate (13.1 mL, 138 mmol, 1.20 equiv) was added dropwise via syringe to a stirred heterogeneous mixture of 5-methylvanillin (**90**)[130] (19.1 g, 115 mmol, 1.00 equiv) and potassium carbonate (32.0 g, 232 mmol, 2.01 equiv) in acetone (230 mL) at ambient temperature. After 3.5 h, Et_2O (300 mL) was added to the reaction mixture, which was then filtered and concentrated under reduced pressure. The crude residue was then directly purified by flash column chromatography (silica gel, eluent: gradient, 10% → 20% EtOAc in hexanes) to afford 5-methylveratraldehyde (**S3**) (20.3 g, 98%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 7.30 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 191.4, 153.2, 152.9, 132.4, 132.1, 127.3, 108.8, 60.3, 55.9, 15.9. **FTIR** (thin film) cm^{-1}: 2939, 1695, 1300, 1141, 857, 684. **HRMS** (ESI): calc'd for $C_{10}H_{12}NaO_3$ $[M+Na]^+$: 203.0679, found 203.0673. **TLC** (17% EtOAc in hexanes), R_f: 0.37 (UV, CAM).

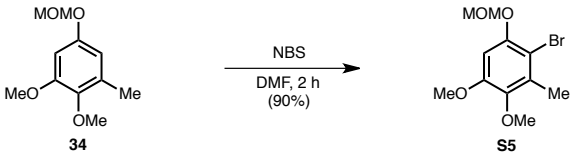
[130] 5-Methylvanillin (**90**) was prepared from vanillin in two steps on multigram scale following literature procedure: Sinhababu, A. K.; Borchardt, R. T. *Syn. Comm.* **1983**, *13*, 677–683.



Trialkoxytoluene 34: A 2-L round-bottom flask was charged with **S3** (20.3 g, 113 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. $NaHCO_3$ (945 mg, 11.3 mmol, 0.100 equiv) and CH_2Cl_2 (225 mL) were sequentially introduced. *m*-CPBA (>95% purity, 23.3 g, 135 mmol, 1.20 equiv) was then added as a single portion to the stirred reaction mixture. After 1 h, MeOH (550 mL) and sodium carbonate (29.8 g, 281 mmol, 2.50 equiv) were sequentially added to the stirred reaction mixture. After stirring for an additional 4 h, the reaction mixture was concentrated under reduced pressure. The crude residue was then re-suspended in water (1 L) and CH_2Cl_2 (500 mL), and cautiously acidified with concentrated hydrochloric acid until pH 4 was reached. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 200 mL). The combined organic layers were then washed with saturated aqueous Na_2SO_3 solution (2 × 250 mL) and saturated aqueous $NaHCO_3$ solution (3 × 250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude phenol **S4** as a faint orange solid, which was used without further purification.

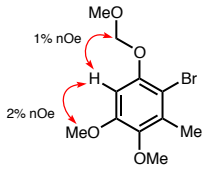
A 1-L flask was charged with crude **S4** and azeotropically dried with three portions of benzene. DMF (300 mL) was introduced, and the resultant solution cooled to 0 °C. Sodium hydride (60% wt. in mineral oil, 5.36 g, 134 mmol, 1.20 equiv) was then added as a single portion to the stirred reaction mixture. After 15 min, the stirred reaction mixture was allowed to warm to ambient temperature. After 45 min, the reaction mixture was re-cooled to 0 °C. Chloromethyl methyl ether (12.2 mL, 161 mmol, 1.43 equiv) was then added dropwise via syringe to the stirred reaction mixture over 5 min. After 30 min, the reaction mixture was allowed to warm to ambient temperature and stirred for an additional 1 h. Water (300 mL) was then slowly added to the stirred reaction mixture, which was then partitioned with Et_2O (300 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 300 mL). The combined organic layers were then washed with

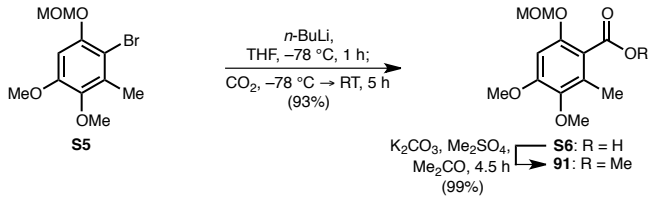
water (3 × 500 mL) and brine (500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 17% EtOAc in hexanes) to afford trialkoxytoluene **34** (21.7 g, 91%) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.47 (d, *J* = 2.7 Hz, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 5.12 (s, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.49 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 153.4, 153.2, 142.3, 132.2, 109.2, 99.6, 94.9, 60.2, 56.0, 55.7, 16.0. **FTIR** (thin film) cm^{-1}: 2936, 1600, 1495, 1225, 1146, 1030, 837, 770. **HRMS** (ESI): calc'd for $C_{11}H_{17}O_4$ $[M+H]^+$: 213.1121, found 213.1119. **TLC** (17% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



Aryl bromide S5: NBS (1.05 g, 5.88 mmol, 1.10 equiv) was added in a single portion to a stirred solution of trialkoxytoluene **34** (1.14 g, 5.35 mmol, 1.00 equiv) in DMF (11 mL). After 2 h, water (25 mL) and Et_2O (25 mL) were added to the stirred reaction mixture, and the layers were separated. The aqueous later was extracted with Et_2O (4 × 25 mL), and the combined organic layers were washed with water (4 × 50 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford aryl bromide **S5** (1.40 g, 90%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 6.69 (s, 1H), 5.20 (s, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 3.54 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 152.1, 150.3, 142.8, 132.8, 106.4, 99.6, 95.8, 60.5, 56.3, 55.9, 16.3. **FTIR** (thin film) cm^{-1}: 2934, 1579, 1475, 1331, 1233, 1151, 1040, 935, 793. **HRMS** (ESI) (*m/z*) calc'd for $C_{11}H_{15}BrO_4Na$ $[M+Na]^+$: 313.0046, found 313.0061. **TLC** (30% EtOAc in hexanes), R_f: 0.44 (UV, anis).

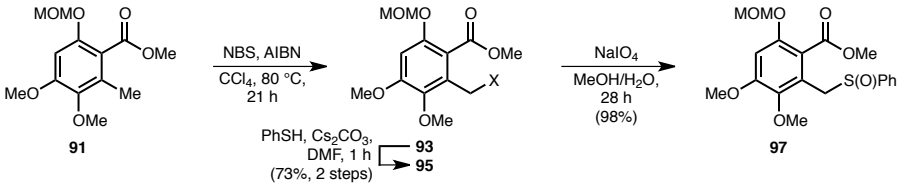
1D NOESY (500 MHz, $CDCl_3$):





<u>*o*-Toluate 91:</u> A solution of *n*-butyllithium in hexanes (2.50 M, 3.11 mL, 7.78 mmol, 1.10 equiv) was added dropwise via syringe to a stirred solution of aryl bromide **S5** (2.06 g, 7.08 mmol, 1.00 equiv) in THF (50 mL) at –78 °C. After 1 h, crushed dry-ice (~5 g) was added in a single portion to the stirred reaction mixture at –78 °C, which after 10 min was allowed to warm to –10 °C. After 2 h, the stirred reaction mixture was allowed to warm to 0 °C. After an additional 1 h, the stirred reaction mixture was allowed to warm to ambient temperature. After an additional 1 h, water (100 mL) and Et_2O (25 mL) were added to the stirred reaction mixture, and the layers were separated. The organic layer was extracted with water (2 × 50 mL). The combined aqueous layers were then acidified to pH 4 with aqueous HCl (1 M) and extracted with EtOAc (4 × 50 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford benzoic acid **S6** (1.69 g, 93%) as a white solid.

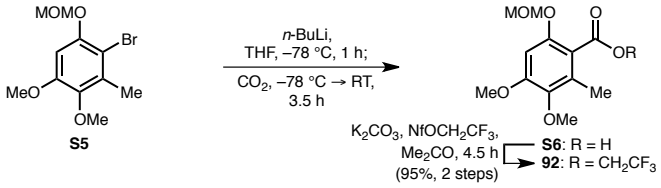
Dimethyl sulfate (621 µL, 6.56 mmol, 1.20 equiv) was added dropwise via syringe to a stirred solution of benzoic acid **S6** (1.40 g, 5.46 mmol, 1.00 equiv) and potassium carbonate (1.51 g, 10.9 mmol, 2.00 equiv) in acetone (16 mL). After 4.5 h, Et_2O (50 mL) was added to the stirred reaction mixture, which was subsequently filtered through a pad of Celite with excess Et_2O. The solution was then concentrated under reduced pressure, and the residue was directly purified by flash column chromatography (silica gel, eluent: gradient, 20% → 25% EtOAc in hexanes) to afford *o*-toluate **91** (99%) as a colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 6.62 (s, 1H), 5.13 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 168.1, 154.1, 150.8, 142.1, 130.1, 117.7, 98.6, 95.5, 60.3, 56.1, 55.8, 52.0, 12.8. **FTIR** (thin film) cm^{-1}: 2995, 1725, 1597, 1489, 1453, 1330, 1266, 1152, 1043, 938, 772. **HRMS** (ESI) (*m/z*) calc'd for $C_{13}H_{18}KO_6$ $[M+K]^+$: 309.0735, found 309.0740. **TLC** (25% EtOAc in hexanes), R_f: 0.33 (UV, anis).



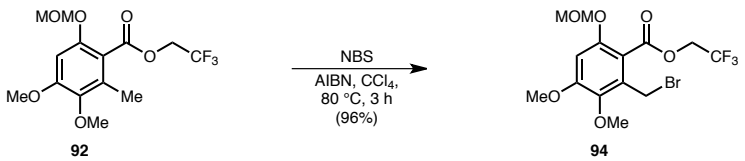
Benzylic sulfoxide 97: NBS (36 mg, 0.19 mmol, 1.1 equiv) was added in a single portion to a stirred solution of *o*-toluate **91** (50 mg, 0.20 mmol, 1.0 equiv) and AIBN (4.0 mg, 0.024 mmol, 0.13 equiv) in CCl_4 (2 mL), and the resultant stirred reaction mixture was refluxed at 80 °C. After 2 h, the stirred reaction mixture was cooled to ambient temperature before additional AIBN (9.1 mg, 0.056 mmol, 0.30 equiv) was added in a single portion. The stirred reaction mixture was then heated to 80 °C. After an additional 4.5 h, the stirred reaction mixture was cooled to ambient temperature before additional NBS (15 mg, 0.084 mmol, 0.46 equiv) was added in a single portion. The stirred reaction mixture was then heated to 80 °C. After an additional 14.5 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was filtered through a pad of Celite. The Celite pad was washed with 1:1 Et_2O/hexanes and the combined organic layers were concentrated. The crude residue was resuspended in 1:1 Et_2O/hexanes and filtered through Celite to remove residual succinimide, and the resultant solution was concentrated under reduced pressure to afford crude benzylic bromide **93**, which was used without further purification.

Cesium carbonate (96 mg, 0.30 mmol, 1.6 equiv) was added in a single portion to a stirred solution of crude **93** and thiophenol (31 µL, 0.30 mmol, 1.6 equiv) in DMF (2 mL). After 1 h, the stirred reaction mixture was diluted with saturated aqueous NH_4Cl solution (5 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 17% EtOAc in hexanes) to afford benzylic phenylsulfide **95** (51 mg, 73%), which was directly used in the next step.

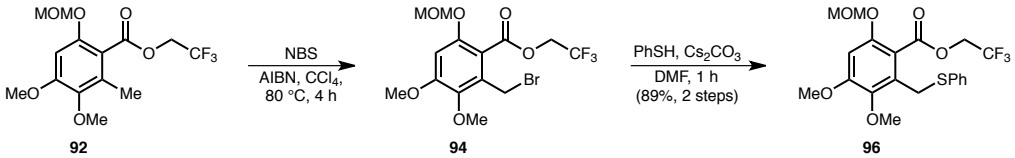
Sodium periodate (35 mg, 0.16 mmol, 1.2 equiv) was added in a single portion to a stirred solution of the benzylic phenylsulfide **95** (51 mg, 0.14 mmol, 1.0 equiv) in 5:1 MeOH/water (1.4 mL). After 23 h, additional sodium periodate (5.8 mg, 0.027 mmol, 0.20 equiv) was added in a single portion to the stirred reaction mixture. After an additional 5 h, the stirred reaction mixture was filtered through a pad of Celite. The pad of Celite was washed with MeOH, and the resultant combined filtrate was concentrated under reduced pressure. The residue was directly purified by flash column chromatography (silica gel, eluent: gradient, 33% → 50 % EtOAc in hexanes) to afford benzylic sulfoxide **97** (52 mg, 98%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.58–7.53 (m, 2H), 7.48–7.43 (m, 3H), 6.74 (s, 1H), 5.11 (dd, *J* = 7.0, 13.2 Hz, 2H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.20 (d, *J* = 12.6 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.3, 154.6, 152.1, 144.0, 143.1, 131.0, 131.0, 128.9, 124.1, 117.0, 101.6, 95.9, 61.2, 56.3, 56.2, 55.8, 52.2. **FTIR** (thin film) cm^{-1}: 2947, 1712, 1594, 1454, 1332, 1267, 1215, 1151, 1085, 1021, 940, 749. **HRMS** (ESI) calc'd for $C_{19}H_{23}O_7S$ $[M+H]^+$: 395.1159, found 395.1161. **TLC** (67% EtOAc in hexanes), R_f: 0.49 (UV, CAM).



***o*-Toluate 92**: A solution of *n*-butyllithium in hexanes (2.63 M, 2.10 mL, 5.51 mmol, 1.15 equiv) was added dropwise via syringe to a stirred solution of aryl bromide **S5** (1.40 g, 4.79 mmol, 1.00 equiv) in THF (48 mL) at –78 °C. After 1 h, crushed dry-ice (~5.5 g) was added in a single portion to the stirred reaction mixture at –78 °C, which after 10 min was allowed to gradually warm to –10 °C over 1 h. After an additional 2 h, the stirred reaction mixture was allowed to warm to ambient temperature. After an additional 30 min, the stirred reaction mixture was concentrated under reduced pressure. DMF (24 mL) and potassium carbonate (1.32 g, 9.58 mmol, 2.00 equiv) were then sequentially introduced into the reaction vessel. 2,2,2-Trifluoroethyl perfluorobutylsulfonate (1.66 mL, 7.19 mmol, 1.50 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 2.5 h, saturated aqueous NH_4Cl solution (25 mL) and Et_2O (50 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with water (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10% → 17% EtOAc in hexanes) to afford *o*-toluate **92** (1.54 g, 95%) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.64 (s, 1H), 5.13 (s, 2H), 4.67 (q, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 3.47 (s, 3H), 2.23 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 165.9, 154.9, 151.6, 142.1, 130.9, 123.0 (q, *J* = 277 Hz), 115.2, 98.2, 95.2, 60.5 (q, *J* = 37 Hz), 60.4, 56.1, 55.8, 12.8. **FTIR** (thin film) cm^{-1}: 2943, 1737, 1595, 1488, 1335, 1257, 1213, 1030, 940. **HRMS** (ESI) calc'd for $C_{14}H_{18}F_3O_6$ $[M+H]^+$: 339.1050, found 339.1053. **TLC** (25% EtOAc in hexanes), R_f: 0.41 (UV, anis).

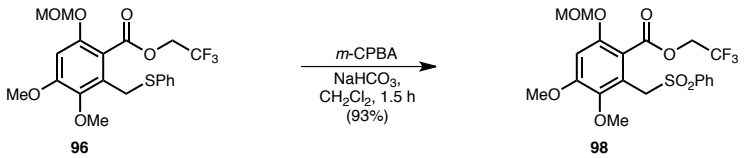


Benzylic bromide 94: NBS (550 mg, 3.09 mmol, 1.20 equiv) was added in a single portion to a stirred solution of *o*-toluate **92** (870 mg, 2.57 mmol, 1.00 equiv) and AIBN (84 mg, 0.51 mmol, 0.20 equiv) in CCl_4 (26 mL), and the resultant reaction mixture was refluxed at 80 °C. After 3 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was filtered through a pad of Celite. The Celite pad was washed with 1:1 Et_2O/hexanes and the combined organic layers were concentrated under reduced pressure in the presence of five drops of Et_3N. The crude residue was directly purified by flash column chromatography (silica gel, eluent: gradient, 10% → 15% EtOAc in hexanes) to yield benzylic bromide **94** (1.03 g, 96%) as a faint yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.76 (s, 1H), 5.13 (s, 2H), 4.70 (q, *J* = 8.5 Hz, 2H), 4.66 (s, 2H), 3.88 (s, 3H), 3.47 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 164.9, 155.2, 152.4, 142.1, 130.9, 123.0 (q, *J* = 278 Hz), 113.9, 100.9, 95.3, 61.0, 60.8 (q, *J* = 37 Hz), 56.1, 55.9, 23.2. **FTIR** (thin film) cm^{-1}: 2941, 1735, 1594, 1483, 1332, 1258, 1144, 1025, 939, 743, 691. **HRMS** (ESI) calc'd for $C_{14}H_{17}BrF_3NaO_6$ $[M+Na]^+$: 438.9975, found 438.9976. **TLC** (25% EtOAc in hexanes), R_f: 0.45 (UV, CAM).

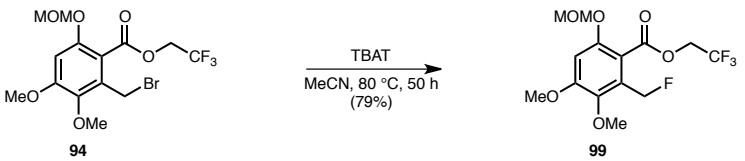


Benzylic phenylsulfide 96: NBS (121 mg, 0.680 mmol, 1.15 equiv) was added in a single portion to a stirred solution of *o*-toluate **92** (200 mg, 0.591 mmol, 1.00 equiv) and AIBN (19.4 mg, 0.118 mmol, 0.20 equiv) in CCl_4 (6 mL), and the resultant reaction mixture was refluxed at 80 °C. After 4 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was filtered through a pad of Celite. The Celite pad was washed with 1:1 Et_2O/hexanes and the combined organic layers were concentrated. The crude residue was resuspended in 1:1 Et_2O/hexanes and filtered through Celite to remove residual succinimide, and the resultant solution was concentrated under reduced pressure to afford crude benzylic bromide **94**, which was used without further purification.

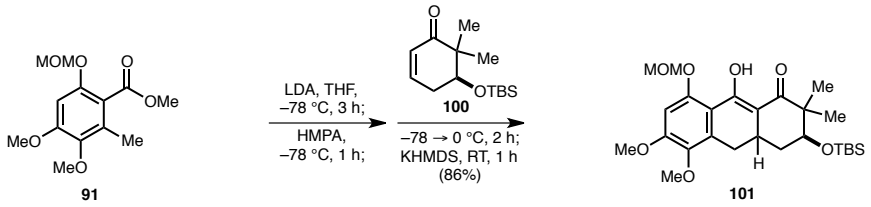
Cesium carbonate (250 mg, 0.768 mmol, 1.30 equiv) was added in a single portion to a stirred solution of crude **94** and thiophenol (114 µL, 0.768 mmol, 1.30 equiv) in DMF (3 mL). After 1 h, the stirred reaction mixture was diluted with water (10 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (4 × 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 11% → 17% EtOAc in hexanes) to afford benzylic phenylsulfide **96** (234 mg, 89%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.40–7.36 (m, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 5.16 (s, 2H), 4.60 (q, *J* = 8.6 Hz, 2H), 4.34 (s, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 3.51 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 165.6, 155.0, 152.4, 142.2, 136.1, 131.3, 130.5, 128.8, 126.6, 123.1 (q, *J* = 277 Hz), 114.3, 99.8, 95.4, 61.4, 60.9 (q, *J* = 37 Hz), 56.2, 55.9, 30.1. **FTIR** (thin film) cm^{-1}: 2943, 1745, 1598, 1491, 1335, 1256, 1149, 1046, 975, 935. **HRMS** (ESI) calc'd for $C_{20}H_{22}F_3O_6S$ $[M+H]^+$: 447.1084, found 447.1088. **TLC** (25% EtOAc in hexanes), R_f: 0.45 (UV, CAM).



Benzylic sulfone 98: A solution of *m*-CPBA (77 wt. %, 75.0 mg, 0.336 mmol, 3.00 equiv) in CH_2Cl_2 (500 µL) was added dropwise via syringe to a stirred solution of benzylic phenylsulfide **96** (50 mg, 0.11 mmol, 1.0 equiv) and $NaHCO_3$ (46 mg, 0.55 mmol, 5.0 equiv) in CH_2Cl_2 (2 mL). After 1.5 h, saturated aqueous Na_2SO_3 solution (5 mL), Et_2O (5 mL), and EtOAc (5 mL) were added to the stirred reaction mixture and the layers were separated. The organic layer was washed with saturated aqueous Na_2SO_3 solution (10 mL), saturated aqueous $NaHCO_3$ solution (3 × 10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford benzylic sulfone **98** (49 mg, 93%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.82 (dd, *J* = 1.2, 8.3 Hz, 2H), 7.62 (tt, *J* = 1.2, 7.6 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 2H), 6.81 (s, 1H), 5.16 (s, 2H), 4.85 (s, 2H), 4.69 (q, *J* = 8.5 Hz, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.51 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 165.6, 155.2, 153.1, 143.4, 139.4, 133.7, 129.0, 128.3, 123.3 (q, *J* = 277 Hz), 121.2, 114.9, 101.9, 95.7, 61.2, 61.1 (q, *J* = 37 Hz), 56.3, 55.9, 52.4. **FTIR** (thin film) cm^{-1}: 2950, 1728, 1595, 1487, 1282, 1151, 1040, 736. **HRMS** (ESI) calc'd for $C_{20}H_{22}F_3O_8S$ $[M+H]^+$: 479.0982, found 479.0985. **TLC** (50% EtOAc in hexanes), R_f: 0.59 (UV, CAM).



Benzylic fluoride 99: TBAT (1.20 g, 2.22 mmol, 2.00 equiv) was added in a single portion to a stirred solution of *o*-toluate **94** (460 mg, 1.11 mmol, 1.00 equiv) in MeCN (11 mL), which was subsequently refluxed at 80 °C. After 50 h, the stirred reaction mixture was cooled to ambient temperature, before saturated aqueous $NaHCO_3$ solution (15 mL) and Et_2O (30 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 25% EtOAc in hexanes) to afford benzylic fluoride **99** (314 mg, 79%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.82 (s, 1H), 5.52 (d, *J* = 47.2 Hz, 2H), 5.15 (s, 2H), 4.67 (q, *J* = 8.6 Hz, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.48 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 165.0, 155.1 (d, *J* = 1.4 Hz), 152.1 (d, *J* = 2.8 Hz), 142.3 (d, *J* = 4.6 Hz), 128.6 (d, *J* = 16 Hz), 123.0 (q, *J* = 277 Hz), 114.2 (d, *J* = 2.8 Hz), 101.4 (d, *J* = 2.8 Hz), 95.3, 76.8 (d, *J* = 165 Hz), 61.8 (d, *J* = 1.4 Hz), 60.8 (q, *J* = 37 Hz), 56.2, 55.9. **FTIR** (thin film) cm^{-1}: 2943, 1745, 1598, 1491, 1335, 1256, 1149, 1046, 975, 935. **HRMS** (ESI) calc'd for $C_{14}H_{17}F_4O_6$ $[M+H]^+$: 357.0956, found 357.0953. **TLC** (25% EtOAc in hexanes), R_f: 0.35 (UV, CAM).

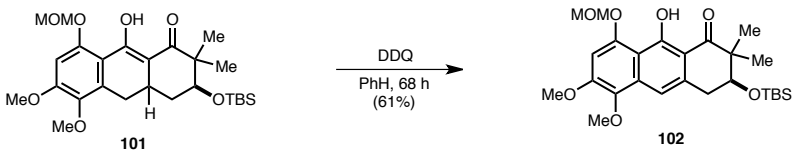


Dihydronaphthalene 101: A solution of *n*-butyllithium in hexanes (2.67 M, 711 µL, 1.90 mmol, 2.50 equiv) was added dropwise via syringe to a stirred solution of diisopropylamine (320 µL, 2.27 mmol, 3.00 equiv) in THF (4 mL) at –78 °C. After 1 h, a solution of *o*-toluate **91** (205 mg, 0.758 mmol, 1.00 equiv) in THF (1 mL) at –78 °C was added dropwise via a dry-ice wrapped cannula to the stirred reaction mixture at –78 °C. The transfer was completed with two additional portions of THF (2 × 500 µL). After an additional 3 h, HMPA (750 µL) was added dropwise via syringe to the stirred reaction mixture at –78 °C. After an additional 1 h, a solution of cyclohexenone **100**[131] (251 mg, 0.990 mmol, 1.30 equiv) in THF (1 mL) at –78 °C was added dropwise via a dry-ice wrapped cannula to the stirred, deep red reaction mixture at –78 °C, whereupon the deep red color quickly dissipated to a faint orange-yellow color. The transfer was completed with two additional portions of THF (2 × 500 µL). The resultant stirred reaction mixture was allowed to slowly warm to 0 °C over 2 h. A solution of KHMDS in toluene (1.0 M, 380 µL, 0.38 mmol, 0.50 equiv) was then added dropwise via syringe to the stirred reaction mixture at 0 °C, which was subsequently allowed to warm to ambient temperature. After an additional 1 h, saturated aqueous NH_4Cl solution (25 mL), Et_2O (25 mL), and EtOAc (25 mL) were added to the stirred reaction mixture. The layers were separated, and the organic layer was washed with water (3 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 6% → 10% EtOAc in hexanes) to afford dihydronaphthalene **101** (319

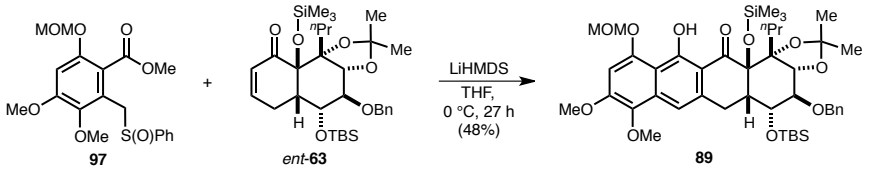
[131] Model cyclohexenone **100** was prepared from the known corresponding cyclohexanone in two steps via (1) trimethylsilylether formation and (2) Saegusa oxidation.

mg, 86%) as a single diastereomer.[132] **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.71 (s, 3H), 5.27 (d, *J* = 6.9 Hz, 1H), 5.22 (d, *J* = 6.9 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 3.70 (d, *J* = 3.4 Hz, 1H), 3.56 (s, 3H), 3.16 (dd, *J* = 4.2, 15.2 Hz, 1H), 2.85 (ddd, *J* = 4.8, 10.4, 19.6 Hz, 1H), 2.17 (t, *J* = 14.8 Hz, 1H), 1.92 (td, *J* = 5.0, 13.4 Hz, 1H), 1.71 (ddd, *J* = 1.5, 11.3, 13.3 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H), 0.83 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 189.1, 185.1, 156.3, 155.5, 140.0, 137.4, 115.6, 106.3, 100.7, 96.6, 74.6, 60.7, 56.5, 55.7, 43.1, 33.7, 29.8, 27.8, 27.6, 25.8, 22.1, 18.1, –4.4, –5.0. **HRMS** (ESI) calc'd for $C_{26}H_{40}NaO_7Si$ $[M+Na]^+$: 515.2436, found 515.2435. **TLC** (25% EtOAc in hexanes), R_f: 0.33 (UV, CAM).

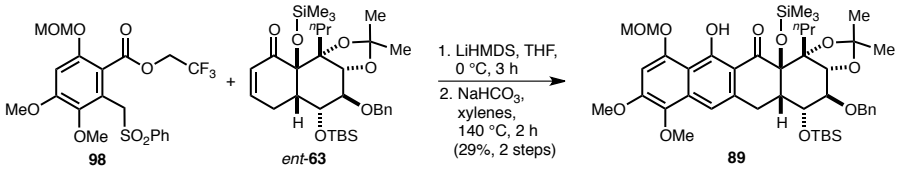
[132] The regioisomer of the enolized 1,3-diketone was not determined and is arbitrarily depicted.



Naphthalene 102: DDQ (12.5 mg, 0.055 mmol, 1.50 equiv) was added in a single portion to a stirred solution of dihydronaphthalene **101** (18 mg, 0.037 mmol, 1.0 equiv) in benzene (1.8 mL). The heterogeneous solution was stirred vigorously and protected from light for 66 h. Saturated aqueous $NaHCO_3$ solution (5 mL) and Et_2O (5 mL) were then added to the stirred reaction mixture. The layers were separated, and the organic layer was washed with water (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 7% → 15% EtOAc in hexanes) to afford naphthalene **102** (11 mg, 61%) as a fluorescent yellow film. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.22 (s, 1H), 6.88 (s, 1H), 5.35–5.29 (m, 2H), 3.99 (s, 3H), 3.96 (dd, *J* = 4.0, 8.4 Hz, 1H), 3.88 (s, 3H), 3.61 (s, 3H), 3.17 (dd, *J* = 3.9, 16.5 Hz, 1H), 3.04 (dd, *J* = 8.2, 16.3 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 0.85 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 208.5, 166.1, 154.4, 152.4, 137.0, 135.2, 134.3, 111.4, 110.1, 108.8, 101.0, 96.9, 74.2, 61.0, 56.5, 56.2, 48.3, 35.4, 25.7, 22.8, 19.8, 18.0, –4.2, –4.9. **FTIR** (thin film) cm^{-1}: 2929, 1619, 1492, 1386, 1341, 1075, 837, 775. **HRMS** (ESI) calc'd for $C_{26}H_{38}NaO_7Si$ $[M+Na]^+$: 513.2280, found 513.2277. **TLC** (25% EtOAc in hexanes), R_f: 0.40 (UV, CAM).

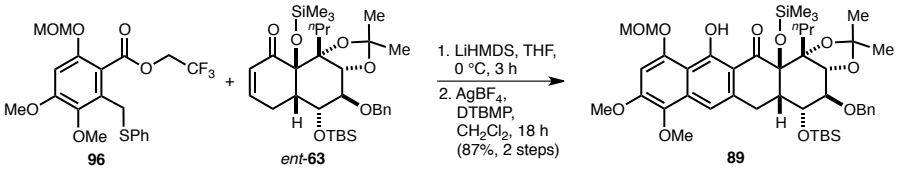


Annulation of Benzylic Sulfoxide 97 with *ent*-63: A 10-mL round-bottom flask was charged with *ent*-**63** (25 mg, 0.042 mmol, 1.0 equiv) and sulfoxide **97** (25 mg, 0.063 mmol, 1.50 equiv), which were azeotropically dried with four portions of benzene. THF (1 mL) was then introduced, and the resultant stirred solution was cooled to 0 °C. A solution of freshly prepared LiHMDS in THF/hexanes (1.0 M, 170 µL, 0.17 mmol, 4.0 equiv) was then added dropwise via syringe to the stirred solution. After 27 h, saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture, which was allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (5 mL) and EtOAc (5 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient 5% → 10% EtOAc in hexanes) to afford naphthol **89** (17 mg, 48%) as a fluorescent yellow-green film. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ: 14.95 (s, 1H), 7.42 (dd, *J* = 0.9, 7.9 Hz, 2H), 7.37–7.33 (m, 2 H), 7.31–7.26 (m, 1H), 7.23 (s, 1H), 6.84 (s, 1H), 5.30 (s, 2H), 4.87 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.26–4.22 (m, 2H), 3.97 (s, 3H), 3.85–3.82 (m, 4H), 3.59 (s, 3H), 3.47 (ddd, *J* = 1.7, 14.3, 16.5 Hz, 2H), 3.19 (dd, *J* = 5.2, 16.9 Hz, 1H), 2.44 (td, *J* = 4.9, 13.9 Hz, 1H), 2.12 (ddd, *J* = 4.2, 12.2, 14.3 Hz, 1H), 1.80 (ddd, *J* = 5.1, 12.0, 14.2 Hz, 1H), 1.61–1.50 (m, 1 H), 1.45–1.37 (m, 1H), 1.26 (s, 3H), 1.13 (s, 3H), 0.93 (s, 9H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.17 (s, 9H), 0.081 (s, 3H), 0.079 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 203.4, 166.8, 155.1, 153.5, 139.4, 139.0, 137.4, 135.2, 128.7, 128.4, 127.9, 111.8, 111.3, 109.9, 109.7, 101.2, 97.3, 87.8, 86.3, 83.3, 81.9, 73.3, 71.7, 61.3, 56.9, 56.8, 49.3, 40.8, 28.0, 27.6, 27.5, 26.3, 18.6, 18.3, 15.3, 2.3, –4.1, –4.2. **FTIR** (thin film) cm^{-1}: 2951, 1734, 1420, 1279, 1215, 1048, 986, 924, 736. **HRMS** (ESI) calc'd for $C_{44}H_{65}O_{11}Si_2$ $[M+H]^+$: 825.4060, found 825.4062. **TLC** (33% EtOAc in hexanes), R_f: 0.30 (UV, CAM).



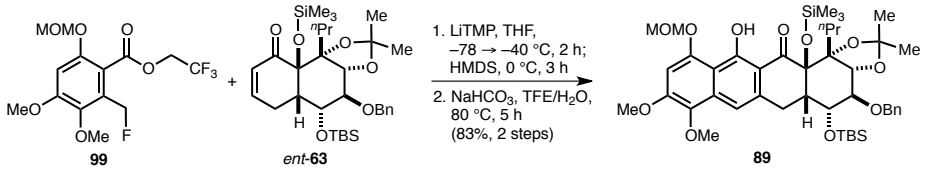
Annulation of Benzylic Sulfone 98 with *ent*-63: A 5-mL round-bottom flask was charged with ***ent*-63** (10.2 mg, 0.0170 mmol, 1.00 equiv) and benzylic sulfone **98** (12.4 mg, 0.0260 mmol, 1.50 equiv), which were azeotropically dried with four portions of benzene. THF (500 μL) was then introduced, and the resultant stirred solution was cooled to 0 °C. A solution of freshly prepared LiHMDS in THF/hexanes (1.0 M, 69 μL, 0.070 mmol, 4.0 equiv) was then added dropwise via syringe to the stirred solution. After 3 h, saturated aqueous NH_4Cl solution (5 mL) was added to the stirred reaction mixture, which was allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (5 mL) and EtOAc (5 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a plug of silica gel (eluent: Et_2O) to afford crude annulated product, which was carried forward without further purification.

A stirred solution of crude annulated product and $NaHCO_3$ (72.5 mg, 0.864 mmol, 50.0 equiv) in xylenes (3 mL) was heated to 140 °C in a sealed vial. After 2 h, the stirred reaction mixture was allowed to cool to ambient temperature before it was filtered and concentrated under reduced pressure. The residue was then directly purified by flash column chromatography (silica gel, eluent: gradient 5% → 10% EtOAc in hexanes) to afford naphthol **89** (4.1 mg, 29%) as a fluorescent yellow-green film. See page 175 for characterization data for **89**.



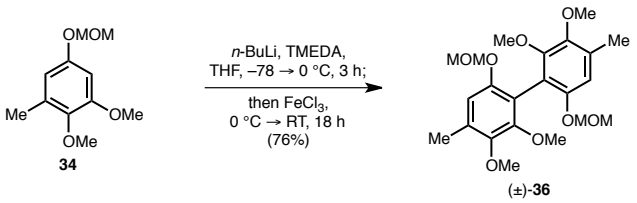
Annulation of Benzylic Phenylsulfide 96 with *ent*-63: A 5-mL round-bottom flask was charged with *ent*-**63** (12.1 mg, 0.0210 mmol, 1.00 equiv) and benzylic phenylsulfide **96** (13.8 mg, 0.0310 mmol, 1.50 equiv), which were azeotropically dried with four portions of benzene. THF (500 μL) was then introduced, and the resultant stirred solution was cooled to 0 °C. A solution of freshly prepared LiHMDS in THF/hexanes (1.0 M, 82 μL, 0.082 mmol, 4.0 equiv) was then added dropwise via syringe to the stirred solution. After 3 h, saturated aqueous NH_4Cl solution (5 mL) was added to the stirred reaction mixture, which was allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (5 mL) and EtOAc (5 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a plug of silica gel (eluent: Et_2O) to afford crude annulated product, which was carried forward without further purification.

Silver(I) tetrafluoroborate (16 mg, 0.082 mmol, 4.0 equiv) was added in a single portion to a stirred solution of crude annulated product and DTBMP (17 mg, 0.082 mmol, 4.0 equiv) in toluene (2 mL) in the dark. After 18 h, saturated aqueous NH_4Cl solution (5 mL), Et_2O (5 mL), and EtOAc (5 mL) were added to the stirred reaction mixture. The layers were separated, and the organic layer was washed with a 9:1 mixture of saturated aqueous NH_4Cl solution and 30% (w/v) NH_4OH solution (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient 5% → 10% EtOAc in hexanes) to afford naphthol **89** (15.7 mg, 87%) as a fluorescent yellow-green film. See page 175 for characterization data for **89**.



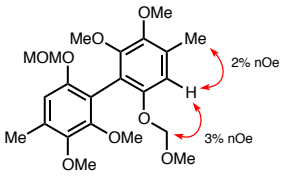
Annulation of Benzylic Fluoride 99 with *ent*-63: A 10-mL round-bottom flask was charged with *ent*-AB-/HG-enone *ent*-**63** (50 mg, 0.085 mmol, 1.0 equiv) and benzylic fluoride **99** (42 mg, 0.120 mmol, 1.4 equiv), which were azeotropically dried with four portions of benzene. THF (2.8 mL) was then introduced, and the resultant stirred solution was cooled to –78 °C. A solution of freshly prepared LiTMP in THF/hexanes (1.0 M, 340 μL, 0.34 mmol, 4.0 equiv) was added dropwise via syringe to the stirred solution. The stirred reaction mixture was allowed to gradually warm from –78 °C to –40 °C over 2 h, at which point HMDS (71 μL, 0.34 mmol, 4.0 equiv) was added dropwise via syringe. The resultant stirred reaction mixture was then allowed to warm to 0 °C. After 3 h, saturated aqueous NH_4Cl solution (5 mL) was added to the stirred reaction mixture, which was allowed to warm to ambient temperature. The resultant mixture was diluted with Et_2O (10 mL) and EtOAc (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a plug of silica gel (eluent: 25% EtOAc in hexanes) to afford crude annulated product, which was carried forward without further purification.

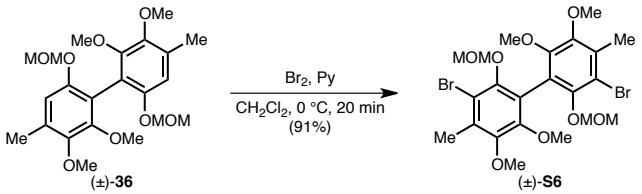
A stirred solution of crude annulated product and $NaHCO_3$ (143 mg, 1.70 mmol, 20.0 equiv) in 19:1 TFE/water (7.4 mL) was heated to 80 °C. After 5 h, the stirred reaction mixture was allowed to cool to ambient temperature before Et_2O (10 mL), hexanes (10 mL), and water (10 mL) were added. The layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 11% → 13% EtOAc in hexanes) to afford naphthalene **89** (58 mg, 83%) as a fluorescent yellow-green film. See page 175 for characterization of **89**.



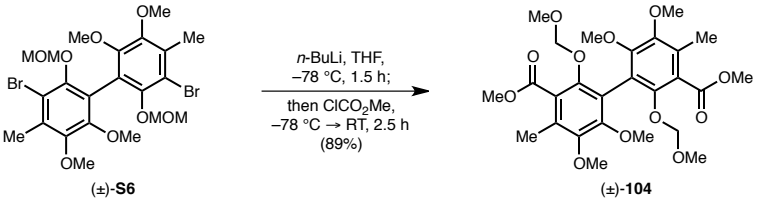
Biaryl (±)-**36**: A 100-mL round-bottom flask was charged with **34** (3.12 g, 14.7 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (25 mL) and TMEDA (2.65 mL, 17.7 mmol, 1.20 equiv) were introduced, and the resultant solution cooled to –78 °C. A solution of *n*-butylithium in hexanes (2.64 M, 6.12 mL, 16.2 mmol, 1.10 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 15 min, the reaction mixture was allowed to warm to 0 °C. After 3 h, a solution of iron(III) chloride (2.87 g, 17.7 mmol, 1.20 equiv) in THF (20 mL) was added via cannula to the stirred reaction mixture over 7 minutes. The transfer was completed with an additional portion of THF (5 mL). After 15 min, the stirred reaction mixture was allowed to warm to ambient temperature. After an additional 18 h, aqueous HCl solution (1.2 M, 50 mL) and Et_2O (100 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with Et_2O (100 mL) and EtOAc (2 × 100 mL). The combined organic layers were then washed with aqueous HCl solution (1.2 M, 100 mL), water (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% → 13% → 17% EtOAc in hexanes) to afford biaryl (±)-**36** (2.35 g, 76%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.78 (s, 2H), 4.98 (s, 4H), 3.80 (s, 6H), 3.67 (s, 6H), 3.33 (s, 6H), 2.31 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 151.6, 151.2, 146.3, 131.5, 117.4, 112.5, 95.3, 60.2, 60.1, 55.7, 16.3. **FTIR** (thin film) cm^{-1}: 2939, 1473, 1394, 1233, 1067, 1017, 927, 738. **HRMS** (ESI) calc'd for $C_{22}H_{30}NaO_8$ $[M+Na]^+$: 445.1838, found 445.1836. **TLC** (20% EtOAc in hexanes), R_f: 0.35 (UV, CAM).

1D NOESY (500 MHz, $CDCl_3$):

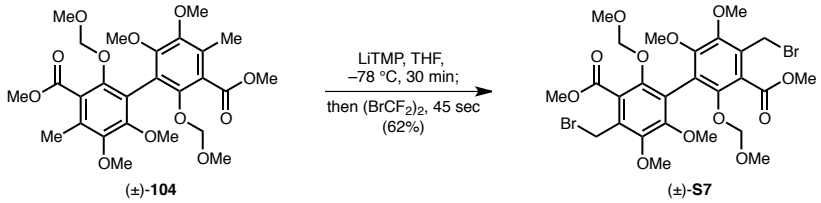




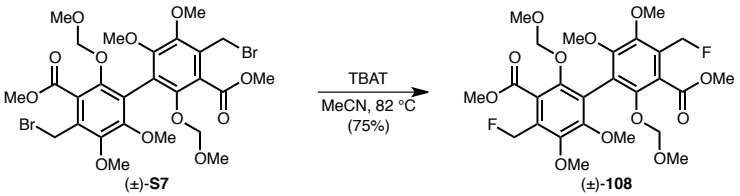
Dibromide (±)-**S6**: A 200-mL round-bottom flask was charged with (±)-**36** (2.35 g, 5.56 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (56 mL) and pyridine (3.38 mL, 41.7 mmol, 7.50 equiv) were introduced, and the resultant solution cooled to 0 °C. A solution of bromine (1.42 mL, 27.8 mmol, 5.00 equiv) in CH_2Cl_2 (13 mL) was then added via syringe down the vessel wall to the stirred reaction mixture. After 20 min, saturated aqueous Na_2SO_3 solution (50 mL) and Et_2O (100 mL) were added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with saturated aqueous $NaHSO_3$ solution (100 mL), aqueous HCl solution (1.2 M, 2 × 100 mL), water (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 9% EtOAc in hexanes) to afford dibromide (±)-**S6** (2.95 g, 91%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.87 (d, *J* = 5.6 Hz, 2H), 4.85 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 6H), 3.75 (s, 6H), 3.03 (s, 6H), 2.42 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 150.8, 148.9, 148.2, 133.0, 122.3, 114.8, 99.1, 60.2, 60.2, 56.6, 16.7. **FTIR** (thin film) cm^{-1}: 2937, 1456, 1387, 1217, 1158, 1098, 1006, 930. **HRMS** (ESI) calc'd for $C_{22}H_{29}Br_2O_8$ $[M+H]^+$: 579.0229, found 579.0223. **TLC** (17% EtOAc in hexanes), R_f: 0.39 (UV, CAM).



Bis-*o*-toluate (±)-**104**: A 200-mL round-bottom flask was charged with (±)-**S6** (3.86 g, 6.65 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (60 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of *n*-butyllithium in hexanes (2.50 M, 6.12 mL, 15.3 mmol, 2.30 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 1.5 h, methyl chloroformate (1.54 mL, 19.9 mmol, 3.00 equiv) was added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to gradually warm to ambient temperature over 2.5 h. Saturated aqueous $NaHCO_3$ solution (50 mL) and Et_2O (100 mL) were then added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 17% → 33% EtOAc in hexanes) to afford bis-*o*-toluate (±)-**104** (3.19 g, 89%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.77 (d, *J* = 5.9 Hz, 2H), 4.75 (d, *J* = 5.9 Hz, 2H), 3.88 (s, 6H), 3.78 (s, 6H), 3.76 (s, 6H), 3.07 (s, 6H), 2.26 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 168.1, 152.8, 148.7, 147.8, 130.2, 125.3, 121.4, 100.0, 60.2, 60.0, 56.5, 52.2, 13.1. **FTIR** (thin film) cm^{-1}: 2949, 1732, 1454, 1393, 1213, 1007, 930, 738. **HRMS** (ESI) calc'd for $C_{26}H_{34}NaO_{12}$ $[M+Na]^+$: 561.1948, found 561.1943. **TLC** (33% EtOAc in hexanes), R_f: 0.35 (UV, CAM).

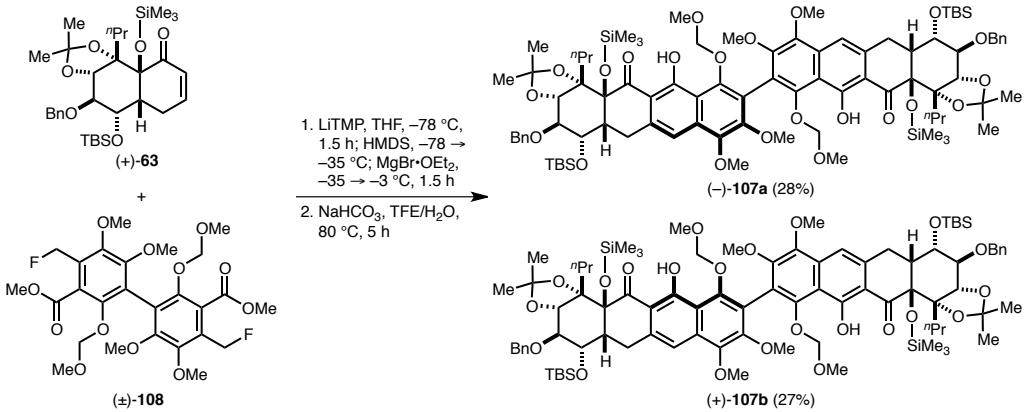


Bis-benzyl bromide (±)-**S7**: A 50-mL round-bottom flask was charged with (±)-**104** (274 mg, 509 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (17 mL) was introduced, and the resultant solution cooled to –78 °C. In a separate 10-mL round-bottom flask, a solution of *n*-butyllithium in hexanes (2.69 M, 567 μL, 1.53 mmol, 3.00 equiv) was added dropwise via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (283 μL, 1.68 mmol, 3.30 equiv) in THF (2.1 mL) at 0 °C. After 30 min, the resultant solution of lithium 2,2,6,6-tetramethylpiperidide was cooled to –78 °C and transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of (±)-**104** over 5 min. The transfer was completed with an additional portion of THF (2 mL). After 30 min, 1,2-dibromotetrafluoroethane (250 μL, 2.10 mmol, 4.12 equiv) was added rapidly via syringe to the vigorously stirred deep red reaction mixture, whereupon the reaction mixture turned colorless. After 45 sec, saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were then washed with saturated aqueous NH_4Cl solution (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in CH_2Cl_2) to afford bis-benzyl bromide (±)-**S7** (219 mg, 62%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.81 (d, J = 6.0 Hz, 2H), 4.78 (d, J = 6.0 Hz, 2H), 4.71 (d, J = 9.8 Hz, 2H), 4.64 (d, J = 9.8 Hz, 2H), 3.94 (s, 6H), 3.93 (s, 6H), 3.79 (s, 6H), 3.01 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 166.9, 153.0, 149.7, 147.9, 130.7, 124.6, 124.5, 100.6, 60.6, 60.1, 56.5, 52.6, 23.8. **FTIR** (thin film) cm^{-1}: 2949, 1729, 1453, 1392, 1225, 1016, 927, 738. **HRMS** (ESI) calc'd for $C_{26}H_{36}Br_2NO_{12}$ $[M+NH_4]^+$: 712.0604, found 712.0580. **TLC** (33% EtOAc in hexanes), R_f: 0.43 (UV, CAM).



(±)-**S7** (±)-**108**

Bis-benzyl fluoride (±)-**108**: A 15-mL round-bottom flask was charged with (±)-**S7** (219 mg, 315 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. The flask was equipped with a reflux condenser and then purged with argon before MeCN (3.1 mL) was introduced. TBAT (850 mg, 1.57 mmol, 5.00 equiv) was then added in a single portion to the stirred reaction mixture, which was subsequently heated to 82 °C. After 18 h, saturated aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 20% → 25% EtOAc in hexanes) to afford bis-benzyl fluoride (±)-**108** (135 mg, 75%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 5.52 (dd, *J* = 48, 1.8 Hz, 2H), 4.80 (s, 4H), 3.90 (s, 6H), 3.86 (s, 6H), 3.79 (s, 6H), 3.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.0, 153.0, 149.5 (d, *J* = 1.8 Hz), 148.3 (d, *J* = 3.7 Hz), 128.3 (d, *J* = 15.6 Hz), 125.2 (d, *J* = 2.7 Hz), 124.9 (d, *J* = 3.7 Hz), 100.5, 77.0 (d, *J* = 165 Hz), 61.4, 60.2, 56.6, 52.6. **FTIR** (thin film) cm^{-1}: 2951, 1734, 1420, 1279, 1215, 1048, 986, 924, 736. **HRMS** (ESI) calc'd for $C_{26}H_{32}F_2NaO_{12}$ $[M+Na]^+$: 597.1760, found 597.1735. **TLC** (33% EtOAc in hexanes), R_f: 0.30 (UV, CAM).



Protected HMP-Y1 (–)-**107a and atrop-HMP-Y1** (+)-**107b**: A 10-mL round-bottom flask was charged with (±)-**108** (26.4 mg, 0.046 mmol, 1.00 equiv) and (+)-**63** (59.5 mg, 0.100 mmol, 2.20 equiv) and azeotropically dried with four portions of benzene. THF (1 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of *n*-butyllithium in hexanes (2.42 M, 95.0 µL, 0.230 mmol, 5.00 equiv) was added via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (42.3 µL, 0.250 mmol, 5.43 equiv) in THF (0.46 mL) at –78 °C in a 5-mL round-bottom flask. The resultant solution was allowed to warm to 0 °C. After 30 min, the solution of lithium 2,2,6,6-tetramethylpiperidide was cooled to –78 °C and transferred dropwise to the stirred, cooled solution of (±)-**108** and (+)-**63** via a dry-ice wrapped cannula. The transfer was completed with one additional portion of THF (0.10 mL). After 1.5 h, HMDS (48.0 µL, 0.230 mmol, 5.00 equiv) was added to the stirred, light orange reaction mixture, which was then allowed to warm to –35 °C. After 30 min, a solution of freshly prepared magnesium bromide diethyletherate in 2:1 Et_2O/PhH (1.00 M, 83.0 µL, 0.083 mmol, 1.80 equiv) was added dropwise to the stirred reaction mixture, which was then allowed to warm to –3 °C. After 1.5 h, saturated aqueous NH_4Cl solution (1 mL) and EtOAc (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (10 mL), water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then quickly passed through a plug of silica gel (eluent: 15% EtOAc in hexanes) and concentrated under reduced pressure.

The crude product was then resuspended in 2,2,2-trifluoroethanol (3.5 mL) and water (0.18 mL). $NaHCO_3$ (77.3 mg, 0.92 mmol, 20.0 equiv) was then added to the stirred solution, which was subsequently heated to 80 °C. After 5 h, water (5 mL) and EtOAc (25 mL) were added to the orange reaction mixture, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The orange residue was then purified by flash column chromatography (silica gel, eluent: 6% → 8% EtOAc in hexanes) to yield protected HMP-Y1 (–)-**107a** (21 mg, 28%) and protected atrop-HMP-Y1 (+)-**107b** (20.8 mg, 27%) as fluorescent yellow oils.[133]

Protected HMP-Y1 (–)-107a: **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 14.84 (s, 2H), 7.43 (d, *J* = 7.3 Hz, 4H), 7.39 (s, 2H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.3 Hz, 2H), 5.01 (d, *J* = 6.1 Hz, 2H), 4.94 (d, *J* = 6.1 Hz, 2H), 4.87 (d, *J* = 11.6 Hz, 2H), 4.70 (d, *J* = 11.6 Hz, 2H), 4.31 (d, *J* = 3.4 Hz, 2H), 4.26 (dd, *J* = 4.3, 8.9 Hz, 2H), 3.92 (s, 6H), 3.91 (s, 6H), 3.86 (dd, *J* = 3.2, 8.7 Hz, 3H), 3.55 (t, *J* = 15.4 Hz, 2H), 3.26 (dd, *J* = 5.2, 17.1 Hz, 2H), 2.67 (s, 6H), 2.47 (td, *J* = 4.8, 13.8 Hz, 2H), 2.22 (ddd, *J* = 4.1, 12.1, 14.0 Hz, 2H), 1.75 (ddd, *J* = 4.9, 12.0, 14.0 Hz, 2H), 1.63–1.53 (m, 2H), 1.52–1.43 (m, 2H), 1.28 (s, 6H), 1.06 (s, 6H), 0.95 (s, 18H), 0.92 (t, *J* = 7.5 Hz, 6H), 0.17 (s, 18H), 0.10 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 204.2, 165.3, 153.2, 151.4, 142.6, 139.3, 138.9, 135.5, 128.7, 128.4, 127.9, 123.1, 115.2, 112.7, 110.4, 109.3, 101.3, 87.8, 85.8, 83.4, 82.2, 73.2, 71.8, 61.2, 60.9, 56.3, 49.4, 41.4, 27.6, 27.4, 27.1, 26.3, 18.6, 18.5, 15.3, 2.2, –4.1, –4.2. **FTIR** (thin film) cm^{-1}: 2953, 1616, 1457, 1374, 1252, 1117, 1079, 1034, 844. **HRMS** (ESI) calc'd for $C_{88}H_{127}O_{22}Si_4$ $[M+H]^+$: 1647.7891, found 1647.7880. **$[\alpha]_D^{23}$**: –68 (*c* = 1.24, CH_2Cl_2). **TLC** (20% EtOAc in hexanes), R_f: 0.58 (UV, CAM).

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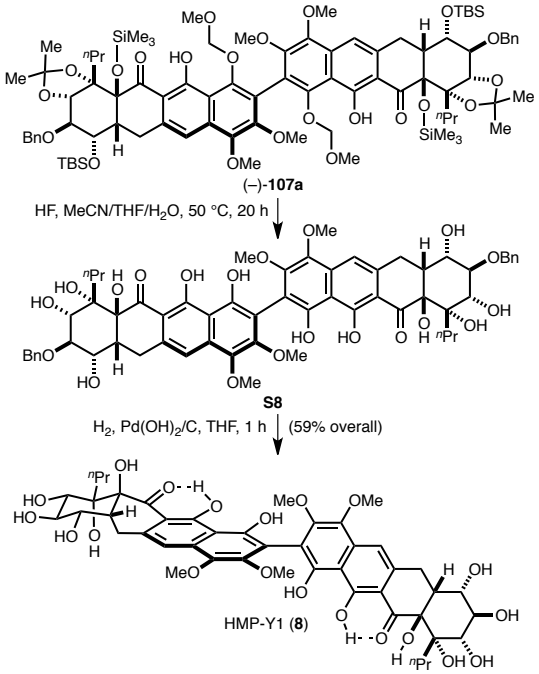
[133] The stereochemistry about the C2–C2' axis of (–)-**107a** and (+)-**107b** is inferred from our assignment of HMP-Y1 (**8**).

Protected atrop-HMP-Y1 (+)-107b: **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 14.73 (s, 2H), 7.43 (d, *J* = 7.6 Hz, 4H), 7.37 (s, 6H), 7.29 (t, *J* = 7.3 Hz, 2H), 5.00 (d, *J* = 6.1 Hz, 2H), 4.95 (d, *J* = 6.1 Hz, 2H), 4.90 (d, *J* = 11.6 Hz, 2H), 4.71 (d, *J* = 11.6 Hz, 2H), 4.28–4.24 (m, 4H), 3.95 (s, 6H), 3.93 (s, 6H), 3.87 (dd, *J* = 4.0, 8.9 Hz, 2H), 3.54 (ddd, *J* = 1.5, 14.0, 16.8 Hz, 2H), 3.25 (dd, *J* = 5.3, 17.2 Hz, 2H), 2.72 (s, 6H), 2.50 (td, *J* = 5.1, 13.7 Hz, 2H), 2.09 (ddd, *J* = 4.0, 12.3, 14.3 Hz, 2H), 1.84 (ddd, *J* = 4.9, 12.0, 14.3 Hz, 2H), 1.28 (s, 6H), 1.19 (s, 6H), 0.95 (s, 18H), 0.88 (t, *J* = 7.3 Hz, 6H), 0.19 (s, 18H), 0.10 (s, 6H), 0.10 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 204.2, 165.2, 153.1, 151.3, 142.5, 139.4, 139.0, 135.6, 128.7, 128.4, 127.9, 123.0, 115.0, 112.8, 110.4, 109.9, 101.3, 87.8, 86.5, 83.3, 82.0, 73.3, 71.7, 61.1, 60.9, 56.6, 49.2, 40.6, 28.1, 27.8, 27.7, 26.3, 18.6, 18.1, 15.2, 2.3, –4.1, –4.2. **FTIR** (thin film) cm^{-1}: 2989, 1616, 1456, 1373, 1252, 1118, 1078, 1036, 843. **HRMS** (ESI) calc'd for $C_{88}H_{126}O_{22}NaSi_4$ $[M+Na]^+$: 1669.7710, found 1669.7619. **$[\alpha]_D^{23}$**: +195 (*c* = 0.94, CH_2Cl_2). **TLC** (20% EtOAc in hexanes), R_f: 0.53 (UV, CAM).

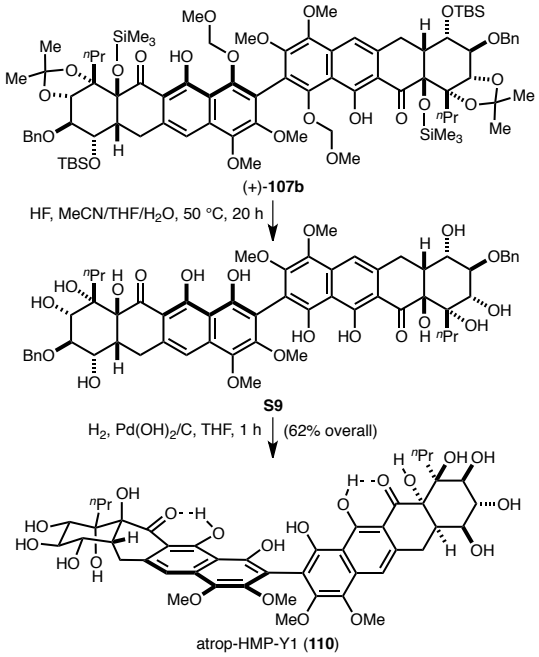


HMP-Y1 (8): Aqueous HF solution (48 wt. %, 3 mL) was slowly added to a stirred solution of (–)-**107a** (9.00 mg, 5.46 μmol, 1.00 equiv) in 1:1 MeCN/THF (6 mL) in a polyethylene vessel and heated to 50 °C. After 20 h, the reaction mixture was cooled to ambient temperature and cautiously poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ solution (50 mL), EtOAc (30 mL), and ice at 0 °C. After gas evolution ceased, the stirred mixture was diluted with EtOAc (50 mL) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered through a cotton plug, and concentrated under reduced pressure to afford crude octacycle **S8** as an orange film, which was used without further purification.

A 50-mL round-bottom flask was charged with a solution of crude **S8** and THF (18.0 mL). Palladium hydroxide on carbon (20 wt. %, 18.0 mg, 25.6 μmol, 4.70 equiv) was added in a single portion to the stirred solution and the reaction mixture was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen for 1 h before the balloon was removed and the stirred reaction mixture was sparged with argon. After 2 min, the mixture was filtered through a 0.2 μm PVDF syringe filter and rinsed with excess methanol to give an

orange-yellow homogeneous solution. The solution was concentrated and the resultant orange film was purified by semi-preparative HPLC on a Cosmosil 5C18-AR-II packed column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: methanol, solvent B: 0.05% (v/v) trifluoroacetic acid in water (pH 2.4), injection volume 300 μL (150 μL 0.05% (v/v) trifluoroacetic acid in water, 150 μL methanol), isocratic elution with 60% A for 20 min, flow rate: 4.0 mL/min]. Fractions eluting at 13–14.5 min were collected and concentrated under reduced pressure to afford HMP-Y1 (**8**) (3.0 mg, 59%) as a yellow film. **^{1}H NMR** (600 MHz, CD_3OD) δ: 7.34 (s, 2H), 4.08 (dd, *J* = 5.5, 9.6 Hz, 2H), 3.94 (t, *J* = 9.4 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 6H), 3.78–3.68 (m, 4H), 3.18 (dd, *J* = 4.6, 16.5 Hz, 2H), 2.66 (dt, *J* = 5.3, 13.3 Hz, 2H), 1.88–1.79 (m, 2H), 1.79–1.65 (m, 4H), 1.44–1.32 (m, 2H), 0.89 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, CD_3OD) δ: 207.3, 165.8, 155.7, 153.7, 140.9, 140.5, 135.3, 113.3, 112.4, 112.3, 110.2, 80.8, 80.2, 76.1, 74.3, 71.8, 61.7, 61.3, 48.4, 39.2, 28.6, 19.4, 15.7. **FTIR** (thin film) cm^{-1}: 3336, 2951, 2923, 2842, 1647, 1451, 1410, 1367, 1236, 1203, 1176, 1016, 847, 783. **HRMS** (ESI) calc'd for $C_{46}H_{54}NaO_{20}$ $[M+Na]^+$: 949.3106, found 949.3084. **TLC** (silica gel RP-18, 45% water in MeCN), R_f: 0.69 (UV).

The stereochemistry about the C2–C2' bond was assigned by comparing the CD spectra of **8** and HMP-Y6 (**9**); the periodicity and shape of the curves showed a high degree of similarity (See Appendix C Figure S15). See Appendix C Table S4–S6 and Figure S12–S14 for further comparison to related natural products.

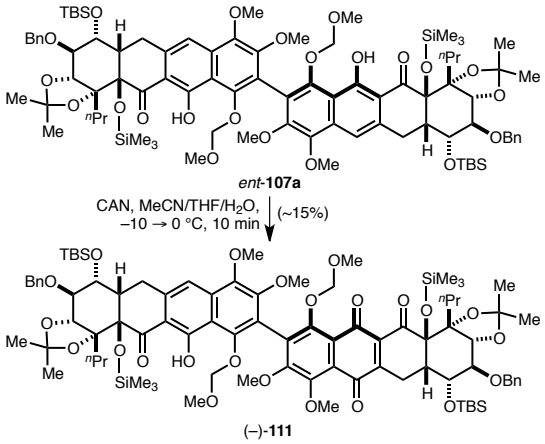


Atrop-HMP-Y1 (110): Concentrated aqueous HF solution (48 wt. %, 3 mL) was slowly added to a stirred solution of (+)-**107b** (12.4 mg, 7.52 μmol, 1.00 equiv) in 1:1 MeCN/THF (6 mL) in a polyethylene vessel and heated to 50 °C. After 20 h, the reaction mixture was cooled to ambient temperature and cautiously poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ solution (50 mL), EtOAc (30 mL), and ice at 0 °C. After gas evolution ceased, the stirred mixture was diluted with EtOAc (50 mL) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered through a cotton plug, and concentrated under reduced pressure to afford crude octacycle **S9** as an orange film, which was used without further purification.

A 50-mL round-bottom flask was charged with crude **S9** and THF (25.0 mL). Palladium hydroxide on carbon (20 wt. % loading, 25.0 mg, 35.6 μmol, 4.70 equiv) was added in a single portion to the stirred solution, which was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen for 1 h before the balloon was removed and the stirred reaction mixture was sparged with argon. After 2 min, the mixture was filtered through a 0.2 μm PVDF syringe filter and rinsed with excess methanol to give an orange-

yellow homogeneous solution. The solution was concentrated and the resultant orange film was purified by semi-preparative HPLC on a Cosmosil 5C18-AR-II column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: methanol, solvent B: 0.05% (v/v) trifluoroacetic acid in water (pH 2.4), injection volume 300 μL (150 μL 0.05% (v/v) trifluoroacetic acid in water, 150 μL methanol), isocratic elution with 60% A for 20 min, flow rate: 4.0 mL/min]. Fractions eluting at 17.5–19.5 min were collected and concentrated under reduced pressure to afford atrop-HMP-Y1 (**110**) (4.3 mg, 62%) as a yellow film. **^{1}H NMR** (600 MHz, CD_3OD) δ: 7.35 (s, 2H), 4.09 (dd, *J* = 5.4, 9.8 Hz, 2H), 3.94 (t, *J* = 9.5 Hz, 2H), 3.88 (s, 6H), 3.83 (s, 6H), 3.77–3.70 (m, 4H), 3.18 (dd, *J* = 5.9, 17.0 Hz, 2H), 2.66 (td, *J* = 5.9, 13.2 Hz, 2H), 1.86–1.79 (m, 2H), 1.79–1.66 (m, 4H), 1.42–1.32 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (126 MHz, CD_3OD) δ: 207.3, 165.8, 155.7, 153.7, 140.8, 140.4, 135.3, 113.2, 112.4, 112.3, 110.2, 80.8, 80.2, 76.1, 74.3, 71.8, 61.7, 61.3, 48.5, 39.2, 28.6, 19.4, 15.8. **FTIR** (thin film) cm^{-1}: 3391, 3006, 2923, 2852, 1656, 1634, 1522, 1457, 1411, 1336, 1206, 1143, 1024, 847, 803. **HRMS** (ESI) calc'd for $C_{46}H_{54}NaO_{20}$ $[M+Na]^+$: 949.3106, found 949.3085. **TLC** (silica gel RP-18, 45% water in MeCN), R_f: 0.72 (UV).

The stereochemistry about the C2–C2' bond was assigned by comparing the CD spectra of **110** and HMP-Y6 (**9**) (Appendix C, Table S4); the periodicity and shape of the curves showed a low degree of similarity (See Appendix C, Figure S15).

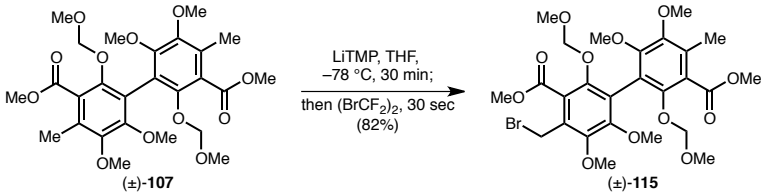


C-ring quinone (–)-**111:** To a stirred solution of binaphthol *ent*-**107a**[134] (12.5 mg, 7.58 μmol, 1.00 equiv) in 3:2:1 MeCN/THF/water (0.75 mL) at –10 °C was added ammonium cerium(IV) nitrate (8.3 mg, 15 μmol, 2.0 equiv) in a single portion. The resultant stirred solution was allowed to warm to 0 °C. After 10 min, the reaction mixture was partitioned with CH_2Cl_2 (2 mL) and saturated aqueous $NaHCO_3$ solution (1 mL), and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 1 mL) and the combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash preparatory thin-layer chromatography [(run 1: eluent: 13% EtOAc in hexanes), (run 2: eluent: 3% EtOAc in benzene)] to afford C-ring quinone (–)-**111** (~1.9 mg, ~15%) as a yellow film. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 14.83 (s, 1 H), 7.44–7.41 (m, 3H), 7.37–7.33 (m, 5H), 7.31–7.27 (m, 2H), 5.06 (d, *J* = 6.3 Hz, 1H), 5.05 (d, *J* = 6.3 Hz, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 5.00 (d, *J* = 6.6 Hz, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 6.3 Hz, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 4.26–4.22 (m, 2H), 4.03 (d, *J* = 6.3 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 3.87–3.82 (m, 2H), 3.52 (dt, *J* = 1.4, 15.3 Hz, 1H), 3.22 (dd, *J* = 5.5, 17.4 Hz, 1H), 3.08–3.00 (m, 4H), 2.92 (dd, *J* = 7.2, 13.2 Hz, 1H), 2.80 (s, 3H), 2.46 (td, *J* = 5.0, 13.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.10 (ddd, *J* = 4.2, 12.4, 14.1 Hz, 1H), 2.04 (ddd, *J* = 5.5, 12.4, 14.7 Hz, 1H), 1.81 (ddd, *J* = 4.7, 12.1, 14.3 Hz, 1H), 1.55–1.48 (m, 2H), 1.32 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.39–1.21 (m, 2H), 1.17 (s, 3H), 1.14–1.07 (m, 1H), 0.94 (s,

[134] *ent*-**107a** was prepared from (±)-**108** and *ent*-**63** following the protocol detailed for (–)-**107a** and (+)-**107b**.

9H), 0.92 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H), 0.22 (s, 9H), 0.16 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 203.6, 198.0, 185.5, 179.2, 164.7, 158.0, 153.7, 151.8, 151.6, 150.3, 149.1, 142.0, 138.7, 138.7, 138.6, 135.9, 135.3, 133.0, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 126.1, 120.9, 114.6, 112.1, 110.7, 109.7, 109.2, 101.5, 101.0, 88.2, 87.2, 86.1, 85.8, 82.5, 81.6, 81.5, 81.3, 73.5, 72.9, 70.9, 70.6, 61.2, 60.9, 60.7, 60.6, 56.6, 56.5, 48.8, 46.4, 40.0, 37.5, 29.3, 28.7, 27.8, 27.5, 27.1, 26.0, 25.9, 24.3, 18.11, 18.09, 17.7, 15.5, 14.9, 14.4, 2.7, 2.0, –4.4, –4.4, –4.6, –4.6.[135] **FTIR** (thin film) cm^{-1}: 2953, 1716, 1667, 1617, 1459, 1378, 1252, 1085, 843. **HRMS** (ESI) calc'd for $C_{88}H_{124}O_{23}Si_4$ $[M+H]^+$: 1661.7683, found 1661.7650. **$[\alpha]_D^{24}$**: –72 (*c* = 0.40, CH_2Cl_2). **TLC** (17% EtOAc in hexanes), R_f: 0.43 (UV, CAM).

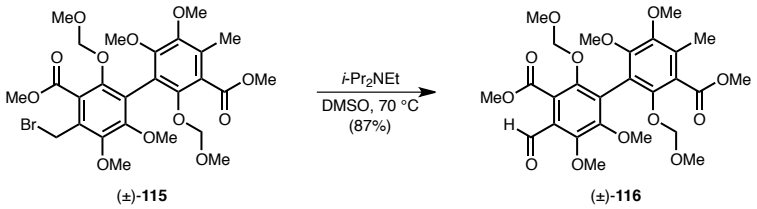
[135] Due to the pseudo-C_2-symmetric nature of (–)-**111**, one carbon resonance of (–)-**111** is unresolved.



(±)-**107** (±)-**115**

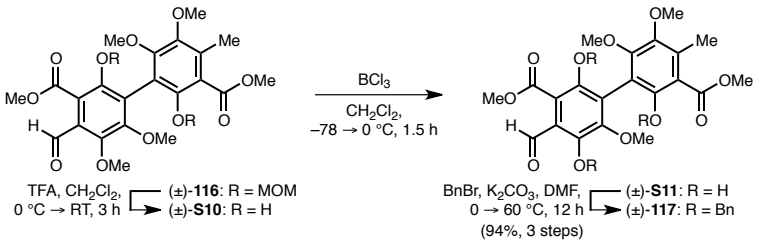
Benzyl bromide (±)-**115**: A 200-mL round-bottom flask was charged with (±)-**107** (996 mg, 1.85 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (62 mL) was introduced, and the resultant solution cooled to –78 °C. In a separate 10-mL round-bottom flask, a solution of *n*-butyllithium in hexanes (2.50 M, 930 μL, 2.33 mmol, 1.26 equiv) was added dropwise via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (421 μL, 2.49 mmol, 1.35 equiv) in THF (3.3 mL) at 0 °C. After 30 min, the solution of lithium 2,2,6,6-tetramethylpiperidide was cooled to –78 °C and transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of (±)-**107** over 5 min. The transfer was completed with an additional portion of THF (3 mL). After 30 min, 1,2-dibromotetrafluoroethane (445 μL, 3.73 mmol, 2.02 equiv) was added rapidly via syringe to the vigorously stirred deep red reaction mixture, whereupon the reaction mixture quickly turned colorless. After 30 sec, saturated aqueous NH_4Cl solution (30 mL) was rapidly added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (100 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL) and the combined organic layers were then washed with saturated aqueous NH_4Cl solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% → 6% EtOAc in CH_2Cl_2) to afford bis-benzyl bromide (±)-**S7** (114 mg, 9%) as a colorless oil and benzyl bromide (±)-**115** (934 mg, 82%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 4.80–4.76 (m, 3H), 4.74 (d, J = 5.6 Hz, 1H), 4.70 (d, J = 9.7 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 168.0, 167.0, 153.2, 152.5, 149.5, 148.9, 147.8, 147.7, 130.7, 130.1, 125.3, 125.1, 124.5, 120.9, 100.4, 100.1, 60.6, 60.2, 60.0, 60.0, 56.6, 56.4, 52.5, 52.2, 23.9, 13.1.

FTIR (thin film) cm^{-1}: 2950, 1731, 1392, 1220, 1017, 928, 738. **HRMS** (ESI) calc'd for $C_{26}H_{37}BrNO_{12}$ $[M+NH_4]^+$: 634.1494, found 634.1498. **TLC** (33% EtOAc in hexanes), R_f: 0.38 (UV, CAM).



(±)-**115** (±)-**116**

Aldehyde (±)-**116**: A 100-mL round-bottom flask was charged with (±)-**115** (2.74 g, 4.44 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before DMSO (90 mL) was introduced. Diisopropylethylamine (2.32 mL, 13.3 mmol, 3.00 equiv) was added dropwise via syringe to the stirred solution at ambient temperature, which was subsequently warmed to 70 °C. After 2 h, the reaction mixture was cooled to ambient temperature before a saturated aqueous NH_4Cl solution (90 mL) was cautiously added to the stirred reaction mixture. The mixture was partitioned with EtOAc (100 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 75 mL) and the combined organic layers were then washed with saturated aqueous NH_4Cl solution (3 × 200 mL), water (3 × 200 mL), and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 20% → 25% → 33% EtOAc in hexanes) to afford aldehyde (±)-**116** (2.13 g, 87%) as a white solid.**^{1}H NMR** (600 MHz, $CDCl_3$) δ: 10.38 (s, 1H), 4.80–4.79 (m, 4H), 3.97 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.78 (s, 6H), 3.03 (s, 3H), 3.03 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 188.5, 167.9, 167.3, 153.2, 152.7, 152.3, 149.4, 148.7, 147.7, 131.6, 131.2, 127.2, 125.3, 123.6, 120.4, 100.5, 100.5, 62.2, 60.4, 60.2, 60.0, 56.6, 56.5, 52.8, 52.3, 13.1. **FTIR** (thin film) cm^{-1}: 2950, 1734, 1694, 1454, 1217, 1031, 928, 739. **HRMS** (ESI) calc'd for $C_{26}H_{36}NO_{13}$ $[M+NH_4]^+$: 570.2181, found 570.2181. **TLC** (33% EtOAc in hexanes), R_f: 0.22 (UV, CAM).



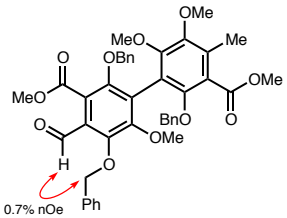
Tribenzyl-Protected Aldehyde (±)-**117**: A 200-mL round-bottom flask was charged with (±)-**116** (2.12 g, 3.83 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (75 mL) was introduced, and the resultant solution cooled to 0 °C. Trifluoroacetic acid (1.48 mL, 19.2 mmol, 5.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. After 2 h, saturated aqueous $NaHCO_3$ solution (100 mL) was added to the stirred reaction mixture. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude bis-phenol (±)-**S10** as a white flocculent solid, which was used without further purification.

A 200-mL round-bottom flask was charged with crude (±)-**S10** and azeotropically dried with three portions of benzene. CH_2Cl_2 (75 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of boron trichloride in CH_2Cl_2 (1.0 M, 15 mL, 15 mmol, 3.9 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C. After 1 h, water (100 mL) and Et_2O (150 mL) were added to the stirred reaction mixture, which was subsequently warmed to ambient temperature. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 75 mL). The combined organic layers were then washed with water (3 × 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude hydroquinone (±)-**S11** as a yellow flocculent solid**,** which was used without further purification.

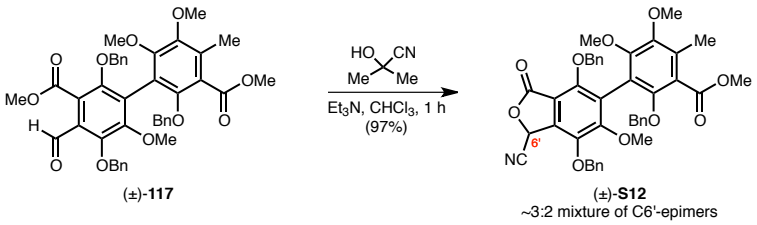
A 200-mL round-bottom flask was charged with crude (±)-**S11** and azeotropically dried with three portions of benzene. DMF (40 mL) was introduced, and the resultant solution cooled to 0 °C. Benzyl bromide (2.28 mL, 19.2 mmol, 5.00 equiv) and potassium carbonate (3.71 g, 26.8 mmol, 7.00

equiv) were then sequentially added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature and then heated to 60 °C. After 12 h the stirred reaction mixture was allowed to cool to ambient temperature before saturated aqueous NH_4Cl solution (100 mL) and Et_2O (100 mL) were added. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 75 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl solution (2 × 200 mL), water (3 × 200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 17% → 20% EtOAc in hexanes) to afford tribenzyl-protected aldehyde (±)-**117** (2.59 g, 94% over three steps) as a white flocculent solid. **^{1}H NMR** (600 MHz, $CDCl_3$) d: 10.20 (s, 1H), 7.34–7.33 (m, 3H), 7.29–7.27 (m, 2H), 7.24–7.18 (m, 6H), 7.03 (dd, *J* = 1.8, 7.9 Hz, 2H), 6.97 (dd, *J* = 2.5, 6.9 Hz, 2H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.88–4.80 (m, 5H), 3.85 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 2.31 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ: 188.4, 168.0, 167.4, 153.4, 152.2, 151.5, 151.1, 150.2, 147.8, 137.2, 136.9, 135.7, 131.5, 131.3, 128.7, 128.7, 128.5, 128.2, 128.1, 127.7, 127.7, 127.6, 127.2, 125.4, 124.0, 120.0, 76.9, 76.8, 76.4, 61.0, 60.5, 60.0, 52.8, 52.3, 13.1.[136] **FTIR** (thin film) cm^{-1}: 2949, 1734, 1694, 1418, 1218, 1016, 739, 700. **HRMS** (ESI) calc'd for $C_{42}H_{44}NO_{11}$ $[M+NH_4]^+$: 738.2909, found 738.2910. **TLC** (25% EtOAc in hexanes), R_f: 0.30 (UV, CAM).

1D NOESY (600 MHz, $CDCl_3$):



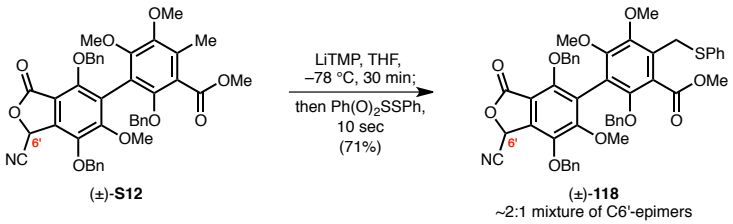
[136] Due to the pseudo-C_2-symmetric nature of (±)-**117** and the presence of multiple benzyl groups, one carbon resonance of a benzyl group of (±)-**117** is unresolved as determined by comparison with related structures.



Cyanophthalide (±)-**S12**: To a solution of (±)-**117** (1.11 g, 1.54 mmol, 1.00 equiv) in chloroform (30 mL) was sequentially added triethylamine (428 µL, 3.07 mmol, 2.00 equiv) and acetone cyanohydrin (280 µL, 3.07 mmol, 2.00 equiv) at ambient temperature. After 1 h, saturated aqueous NH_4Cl solution (30 mL) was added to the reaction mixture, which was stirred vigorously for 5 min. The layers were then separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 20% EtOAc in hexanes) to afford cyanophthalide (±)-**S12** (1.06 g, 97%) as a white flocculent solid (inseparable ~3:2 mixture of C6'-epimers). **^{1}H NMR** (600 MHz, $CDCl_3$, ~3:2 mixture of C6'-epimers; major epimer noted by *) d: 7.40–7.12 (m, 13H*, 13H), 7.01–6.98 (m, 2H), 6.88–6.84 (m, 2H*), 5.45 (s, 1H*), 5.33–5.28 (m, 1H*, 1H), 5.21–5.17 (m, 1H*, 1H), 5.16–5.12 (m, 2H), 5.02 (d, J = 10.8 Hz, 1H*), 4.96–4.92 (m, 1H*, 1H), 4.76–4.70 (m, 1H*, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H*), 3.93 (s, 3H), 3.88 (s, 3H*), 3.88 (s, 3H*), 3.82 (s, 3H), 3.71 (s, 3H*, 3H), 3.68 (s, 3H*, 3H), 2.33 (s, 3H*), 2.32 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 168.0, 168.0, 164.9, 164.8, 158.5, 158.5, 153.5, 153.5, 152.4, 152.3, 150.5, 150.4, 147.8, 147.8, 141.31, 141.26, 137.3, 136.9, 136.7, 136.6, 136.5, 136.4, 135.8, 135.8, 131.1, 131.1, 129.0, 129.0, 128.9, 128.8, 128.8, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.8, 127.8, 127.4, 126.9, 126.8, 126.8, 126.7, 125.3, 125.2, 119.9, 119.9, 113.7, 113.7, 110.8, 110.6, 76.7, 76.6, 76.5, 76.2, 75.2, 74.9, 63.3, 63.3, 61.1, 61.0, 60.5, 60.4, 60.2, 60.1, 52.3, 52.3, 13.1, 13.1.[137] **FTIR** (thin film) cm^{-1}: 2949, 1785, 1731, 1455, 1265, 1004, 737,

[137] Due to the pseudo-C_2-symmetric nature of (±)-**S12**, the presence of multiple benzyl groups, and C6'-epimers, two carbon resonances of the benzyl group(s) of (±)-**S12** are unresolved as determined by comparison with related structures.

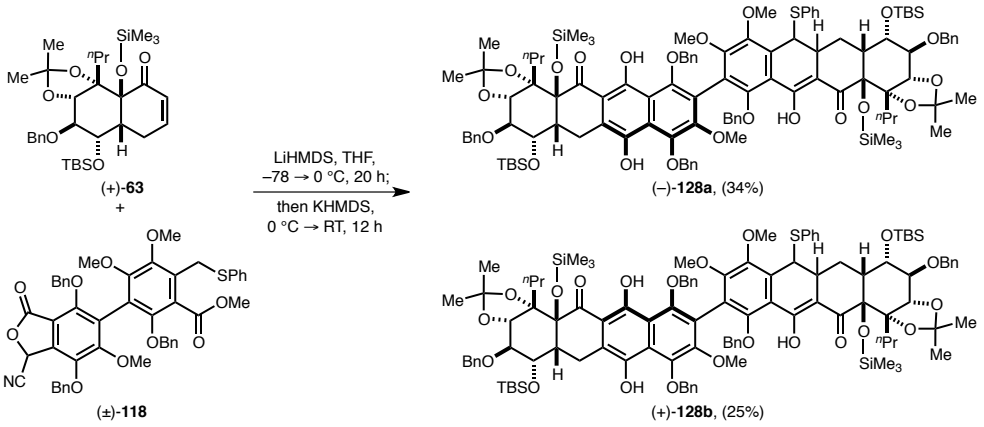
698. **HRMS** (ESI) calc'd for $C_{42}H_{41}N_2O_{10}$ $[M+NH_4]^+$: 733.2756, found 738.2753. **TLC** (25% EtOAc in hexanes), R_f: 0.30 (UV, CAM).



Unsymmetrical biaryl (±)-**118**: A 50-mL round-bottom flask was charged with (±)-**S12** (210 mg, 291 µmol, 1.00 equiv) and azeotropically dried with four portions of benzene. THF (10 mL) was introduced, and the resultant solution cooled to –78 °C. In a separate 10-mL round-bottom flask, a solution of *n*-butyllithium in hexanes (2.56 M, 284 µL, 727 µmol, 2.50 equiv) was added dropwise via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (135 µL, 800 µmol, 2.75 equiv) in THF (1.2 mL) at 0 °C. After 30 min, the resultant solution of lithium 2,2,6,6-tetramethylpiperidide was cooled to –78 °C and transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of (±)-**S12** over 3 min. The transfer was completed with an additional portion of THF (1 mL). After 30 min, a solution of *S*-phenyl benzenethiosulfonate (76.5 mg, 306 µmol, 1.05 equiv) in THF (1.5 mL) was added via syringe rapidly down the vessel wall to the vigorously stirred deep red reaction mixture, whereupon the reaction mixture quickly turns yellow. After 10 sec, a solution of acetic acid (50 µL) in THF (1.0 mL) was rapidly added to the reaction mixture, followed immediately by addition of saturated aqueous NH_4Cl solution (5 mL). The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (20 mL) and EtOAc (20 mL) and the layers were separated. The combined organic layers were then washed with saturated aqueous NH_4Cl solution (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 1% → 2% EtOAc in 9:1 benzene/hexanes) to afford unsymmetrical biaryl (±)-**118** (170 mg, 71%) as a white flocculent solid (inseparable ~2:1 mixture of C6'-epimers). **^{1}H NMR** (600 MHz, $CDCl_3$, ~2:1 mixture of C6'-epimers; major epimer noted by *) d: 7.43–7.14 (m, 13H*, 13H), 6.99 (dd, *J* = 2.3, 5.9 Hz, 2H), 6.85 (dd, *J* = 2.2, 7.2 Hz, 2H*), 5.43 (s, 1H*), 5.33– 5.30 (m, 1H*, 1H), 5.22–**63** (m, 1H*, 1H), 5.17–5.11 (m, 2H), 5.01 (d, *J* = 10.8 Hz, 1H*), 4.94 (d, *J* = 10.8

Hz, 1H*, 1H), 4.76–4.72 (m, 1H*, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H*), 4.41–4.36 (m, 1H*, 1H), 4.33 (d, *J* = 12.0 Hz, 1H*, 1H), 3.92 (s, 3H), 3.86 (s, 3H*), 3.81 (s, 3H*), 3.74 (s, 3H), 3.68 (s, 3H*, 3H), 3.61 (s, 3H), 3.61 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.4, 164.8, 164.8, 158.4, 158.4, 153.4, 153.4, 152.6, 152.5, 151.2, 151.0, 148.0, 148.0, 141.3, 141.3, 137.3, 136.9, 136.7, 136.6, 136.6, 136.6, 136.0, 136.0, 135.8, 135.8, 131.5, 131.3, 131.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.8, 128.8, 128.4, 128.3, 128.1, 128.0, 128.0, 128.0, 127.8, 127.5, 126.9, 126.9, 126.9, 126.6, 126.5, 126.5, 124.6, 124.5, 122.0, 121.9, 113.7, 113.6, 110.9, 110.6, 76.8, 76.7, 76.7, 76.3, 75.2, 74.9, 63.4, 63.3, 61.1, 61.0, 61.0, 61.0, 60.3, 60.3, 52.4, 52.4, 31.0, 30.9.[138] **FTIR** (thin film) cm^{-1}: 2295, 1787, 1730, 1455, 1266, 1027, 739, 699. **HRMS** (ESI) calc'd for $C_{48}H_{41}NNaO_{10}S$ $[M+Na]^+$: 846.2343, found 846.2350. **TLC** (25% EtOAc in hexanes), R_f: 0.30 (UV, CAM).

[138] Due to the pseudo-C_2-symmetric nature of (±)-**118,** the presence of multiple benzyl groups, and epimers at C6', five carbon resonances of the benzyl group(s) and/or benzylic phenylsulfide(s) of (±)-**118** are unresolved as determined by comparison with related structures.



Octacycle (–)-**128a and Octacycle** (+)-**128b**: A 10-mL Schlenk tube was charged with (±)-**118** (66.5 mg, 80.7 µmol, 1.00 equiv) and AB-/HG-enone (+)-**63** (143 mg, 242 µmol, 3.01 equiv), which were then azeotropically dried with five portions of benzene. THF (2.7 mL) was then introduced, and the resultant solution was deoxygenated and then cooled to –78 °C. A solution of freshly prepared deoxygenated lithium hexamethyldisilazide in THF (1.00 M, 807 µL, 807 µmol, 10.0 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 30 min. After 19 h, a solution of deoxygenated potassium hexamethyldisilazide in THF (1.0 M, 2.00 mL, 2.00 mmol, 24.8 equiv) was added dropwise via cannula to the vigorously stirred purple reaction mixture, which was subsequently allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –50 °C before a solution of acetic acid (200 µL) in THF (1.0 mL) was added via syringe rapidly down the vessel-wall to the vigorously stirred purple reaction mixture. After the reaction mixture turned fluorescent orange, a saturated aqueous NH_4Cl solution (2 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (20 mL), hexanes (20 mL) and saturated aqueous NH_4Cl solution (10 mL), and the layers were separated. The organic layers were then washed with saturated aqueous NH_4Cl solution (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 6% → 10% EtOAc in hexanes)

to afford octacycle (–)-**128a**[139] (53.0 mg, 34%) as an orange flocculent solid and impure octacycle (+)-**128b**. The mixture containing (+)-**128b** was further purified by preparatory thin-layer chromatography (eluent: 10% EtOAc in hexanes) to afford octacycle (+)-**128b**[139,140] (38.9 mg, 25%) as an orange flocculent solid.[141]

Octacycle (–)-**128a**: **^{1}H NMR** (600 MHz, CD_2Cl_2) d: 17.39 (s, 1H), 14.22 (s, 1H), 9.45 (s, 1H), 7.46–7.39 (m, 9H), 7.39–7.32 (m, 6H), 7.31–7.27 (m, 2H), 7.25–7.20 (m, 3H), 7.19–7.15 (m, 3H), 7.07 (m, 1H), 7.01–6.98 (m, 2H), 6.96–6.93 (m, 4H), 5.13 (d, *J* = 11.2 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.94–4.89 (m, 4H), 4.81 (d, *J* = 3.8 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 10.6 Hz, 1H), 4.29–4.23 (m, 3H), 4.16 (d, *J* = 5.9 Hz, 1H), 3.95 (dd, *J* = 3.8, 9.0 Hz, 1H), 3.90 (s, 3H), 3.87 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.54 (s, 3H), 3.40–3.34 (m, 2H), 3.24 (s, 3H), 3.09 (dd, *J* = 13.3, 18.0 Hz, 1H), 2.73–2.67 (m, 1H), 2.55 (dt, *J* = 10.6, 14.5 Hz, 1H), 2.47–2.38 (m, 2H), 2.08–1.96 (m, 2H), 1.96–1.83 (m, 2H), 1.66–1.51 (m, 5H), 1.42–1.32 (m, 8H), 1.27 (s, 3H), 0.96 (s, 9H), 0.92 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.27 (s, 9H), 0.20 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.3, 189.4, 182.5, 157.4, 155.4, 154.6, 154.2, 151.9, 145.4, 142.4, 140.8, 139.6, 139.3, 138.4, 138.4, 138.2, 135.6, 135.5, 133.8, 129.5, 129.4, 129.2, 128.8, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 127.7, 127.6, 127.5, 127.4, 124.8, 124.4, 122.6, 120.5, 120.0, 117.1, 112.8, 110.6, 109.6, 107.3, 107.3, 88.0, 87.6, 87.4, 86.5, 83.5, 82.9, 81.8, 79.3, 77.6, 76.0, 76.0, 73.6, 73.3, 71.8, 71.5, 61.5, 60.3, 60.3, 50.9, 47.8, 47.3, 40.5, 38.8, 34.3, 29.5, 28.9, 28.1, 27.5, 26.3, 26.0, 24.1, 21.4, 18.5, 18.4, 17.9, 17.6, 15.0,

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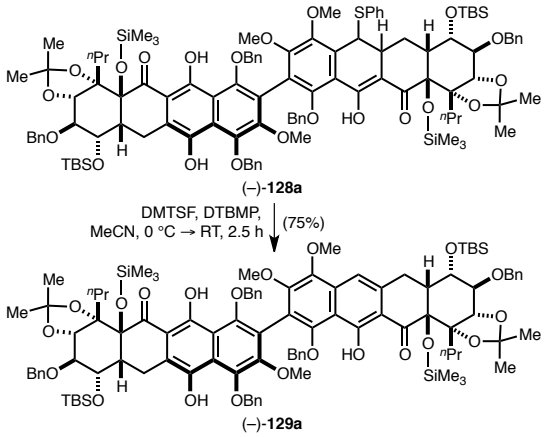
[139] Minor oxidation of (–)-**128a** and (+)-**128b** occurs during purification and handling. Purification of highly oxygenated naphthalenes by flash column chromatography is difficult due to their adherence to silica gel (streaking).

[140] A significant loss of material is observed upon purification of highly oxygenated naphthalenes utilizing preparatory thin-layer chromatography (as determined by purification of pure material), but was necessary to purify (+)-**128b**. It was later determined that minor impurities could be carried forward and removed more easily at subsequent stages without severe detriment to the overall yield.

[141] The stereochemistry about the C2–C2' axis of (–)-**128a**, (+)-**128b**, and further intermediates was inferred from the stereochemistry of hibarimicinone (**6**), which was unambiguously assigned by Tatsuta et al. by total synthesis. See ref. 77.

14.8, 2.5, 2.2, –4.1, –4.2, –4.4, –4.5. **FTIR** (thin film) cm^{-1}: 3364, 2953, 1624, 1594, 1370, 1251, 1078, 843, 740, 698. **HRMS** (ESI) calc'd for $C_{110}H_{141}O_{21}SSi_4$ $[M+H]^+$: 1941.8758, found 1941.8776. $[\alpha]_D^{23}$: –119 (*c* = 0.40, CH_2Cl_2). **TLC** (13% EtOAc in hexanes), R_f: 0.55 (UV, CAM).

Octacycle (+)-**128b**: **^{1}H NMR** (600 MHz, CD_2Cl_2) d: 17.35 (s, 1H), 14.20 (s, 1H), 9.46 (s, 1H), 7.45–7.39 (m, 9H), 7.38–7.32 (m, 8H), 7.31–7.27 (m, 2H), 7.27–7.24 (m, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 7.16 (d, *J* = 1.3 Hz, 1H), 7.11 (tt, *J* = 1.3, 7.5 Hz, 1H), 7.08–7.05 (m, 3H), 7.04–6.99 (m, 4H), 5.12–5.07 (m, 2H), 5.06 (d, *J* = 10.8 Hz, 1H), 5.02 (d, *J* = 10.6 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 10.6 Hz, 1H), 4.81 (d, *J* = 10.4 Hz, 1H), 4.77 (d, *J* = 3.8 Hz, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.29 (dd, *J* = 4.6, 9.0 Hz, 1H), 4.25–4.22 (m, 2H), 4.17 (d, *J* = 5.7 Hz, 1H), 3.93 (dd, *J* = 4.4, 9.0 Hz, 1H), 3.86 (dd, *J* = 5.8, 9.4 Hz, 1H), 3.83 (s, 3H), 3.59 (s, 3H), 3.42–3.36 (m, 2H), 3.16 (s, 3H), 3.07 (dd, *J* = 13.3, 17.9 Hz, 1H), 2.71 (ddd, *J* = 4.5, 7.9, 13.3 Hz, 1H), 2.56–2.43 (m, 3H), 2.05–1.94 (m, 3H), 1.89 (ddd, *J* = 5.1, 12.0, 14.3 Hz, 1H), 1.66–1.58 (m, 1H), 1.54–1.51 (m, 4H), 1.41 (s, 3H), 1.40–1.32 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.96 (s, 9H), 0.92 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.27 (s, 9H), 0.21 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.5, 190.2, 182.5, 157.6, 155.6, 154.6, 154.1, 152.2, 145.4, 142.5, 141.1, 139.8, 139.6, 139.2, 138.7, 138.5, 135.7, 134.7, 134.3, 129.8, 129.6, 129.4, 129.2, 128.7, 128.6, 128.4, 128.4, 128.4, 128.4, 128.2, 127.9, 127.81, 127.75, 127.7, 127.7, 125.0, 124.7, 122.6, 120.8, 120.0, 117.2, 113.1, 110.8, 110.1, 107.6, 107.6, 88.1, 87.7, 87.6, 87.0, 83.6, 83.2, 81.8, 79.6, 77.8, 76.4, 76.3, 73.8, 73.6, 71.9, 71.7, 61.7, 60.5, 60.4, 51.6, 48.1, 47.4, 40.3, 39.2, 34.3, 29.6, 28.9, 28.5, 27.9, 26.4, 26.3, 24.4, 21.7, 18.6, 18.6, 18.0, 18.0, 15.2, 15.0, 2.6, 2.4, –3.9, –4.0, –4.2, –4.3. **FTIR** (thin film) cm^{-1}: 3364, 2967, 1624, 1591, 1379, 1252, 1077, 1006, 842, 739, 698. **HRMS** (ESI) calc'd for $C_{110}H_{141}O_{21}SSi_4$ $[M+H]^+$: 1941.8758, found 1941.8795. $[\alpha]_D^{23}$: +45 (*c* = 0.37, CH_2Cl_2). **TLC** (13% EtOAc in hexanes), R_f: 0.38 (UV, CAM).

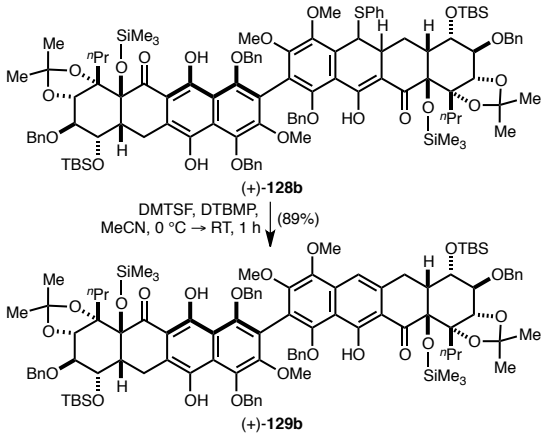


Binaphthalene (–)-**129a**: A 25-mL round-bottom flask was charged with (–)-**128a** (30.0 mg, 15.4 µmol, 1.00 equiv) and DTBMP (15.9 mg, 77.2 µmol, 5.00 equiv) and was then azeotropically dried with five portions of benzene. MeCN (3.5 mL) was introduced, and the resultant solution cooled to 0 °C. A solution of DMTSF (6.05 mg, 30.9 µmol, 2.00 equiv) in MeCN (200 µL) was then added dropwise via syringe to the stirred reaction mixture. The transfer was completed with two additional portions of MeCN (100 µL). After 105 min, an additional portion of DMTSF (3.03 mg, 15.5 µmol, 1.00 equiv) in MeCN (200 µL) was added dropwise via syringe to the stirred reaction mixture. The transfer was completed with two additional portions of MeCN (100 µL). After 15 min, the stirred reaction mixture was allowed to warm to ambient temperature. After 30 min, saturated aqueous $NaHCO_3$ solution (5 mL) was added to the stirred reaction mixture. The mixture was partitioned with Et_2O (10 mL) and hexanes (10 mL) and the layers were separated. The organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 3% → 5% EtOAc in hexanes) to afford binaphthalene (–)-**129a**[142] (21.3 mg, 75%) as an orange film. **^{1}H NMR** (600 MHz, CD_2Cl_2) d: 14.93 (s, 1H), 14.25 (s, 1H), 9.51 (s, 1H), 7.45–7.36 (m, 13H), 7.33–7.28 (m, 2H), 7.11–7.00 (m, 8H), 6.94 (d, *J* = 6.9 Hz, 2H), 5.13 (d, *J* = 10.9 Hz, 1H), 5.08–5.01 (m, 4H), 4.91 (d, *J* = 4.7 Hz, 1H), 4.89 (d, *J*

[142] Minor oxidation of (–)-**129a** occurs during purification and handling. Minor etherification to (–)-**130a** is also observed.

= 4.7 Hz, 1H), 4.73–4.71 (m, 3H), 4.32 (d, *J* = 3.4 Hz, 1H), 4.31–4.26 (m, 3H), 3.96 (dd, *J* = 4.0, 8.7 Hz, 1H), 3.89 (dd, *J* = 3.6, 8.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.62 (ddd, *J* = 1.2, 14.5, 16.4 Hz, 1H), 3.39 (dd, *J* = 6.2, 18.1 Hz, 1H), 3.29 (dd, *J* = 5.0, 17.1 Hz, 1H), 3.10 (dd, *J* = 13.4, 18.1 Hz, 1H), 2.50 (td, *J* = 4.9, 13.8 Hz, 1H), 2.43 (ddd, *J* = 4.7, 5.9, 13.4 Hz, 1H), 2.21 (ddd, *J* = 3.9, 11.9, 14.4 Hz, 1H), 2.05 (ddd, *J* = 4.0, 12.1, 14.3 Hz, 1H), 1.87 (ddd, *J* = 5.1, 12.1, 14.2 Hz, 1H), 1.79 (ddd, *J* = 5.0, 11.9, 14.2 Hz, 1H), 1.63–1.45 (m, 3H), 1.45–1.37 (m, 1H), 1.32 (s, 6H), 1.27 (s, 3H), 1.21 (s, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.21 (s, 9H), 0.19 (s, 9H), 0.11 (s, 6H), 0.10 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.1, 204.0, 165.2, 157.4, 154.1, 152.9, 152.4, 152.2, 142.7, 142.3, 140.7, 139.2, 139.0, 138.8, 138.4, 138.3, 135.5, 135.3, 129.4, 129.2, 129.0, 128.4, 128.3, 128.1, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 124.2, 123.3, 121.9, 120.1, 116.9, 115.9, 112.6, 112.6, 110.2, 109.5, 109.1, 87.5, 87.3, 86.4, 85.6, 83.3, 83.1, 81.9, 81.6, 77.5, 75.9, 75.7, 73.1, 72.9, 71.7, 71.5, 61.3, 60.9, 60.8, 49.1, 47.7, 40.9, 40.3, 27.9, 27.4, 27.3, 27.3, 27.2, 25.9, 25.9, 21.2, 21.2, 18.2, 18.2, 18.1, 17.7, 15.0, 14.9, 2.1, 1.9, –4.3, –4.4, –4.6, –4.7.[143] **FTIR** (thin film) cm^{-1}: 3359, 2952, 1618, 1590, 1371, 1252, 1076, 1035, 844, 698. **HRMS** (ESI) calc'd for $C_{104}H_{135}O_{21}Si_4$ $[M+H]^+$: 1831.8567, found 1831.8516. **$[\alpha]_D^{23}$**: –148 (*c* = 0.40, CH_2Cl_2). **TLC** (13% EtOAc in hexanes), R_f: 0.58 (UV, CAM).

[143] Due to the pseudo-C_2-symmetric nature of (–)-**129a** and the presence of multiple benzyl groups, two carbon resonances of the benzyl group(s) of (–)-**129a** are unresolved as determined by comparison with related structures.

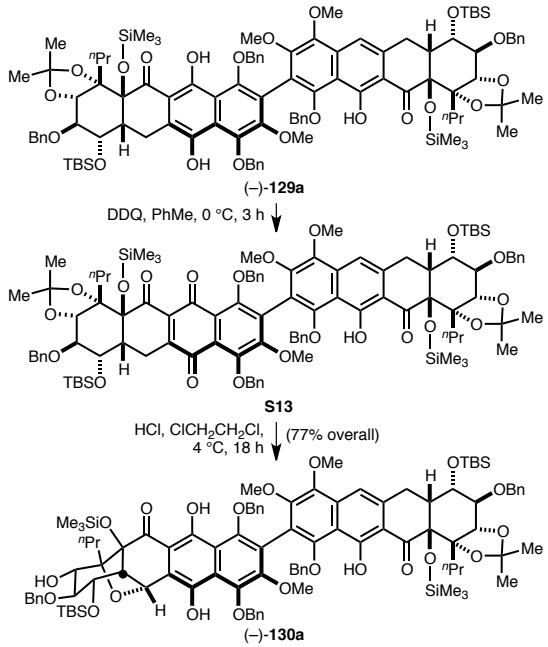


Binaphthalene (+)-**129b**: A 25-mL round-bottom flask was charged with (+)-**128b** (32.0 mg, 16.5 µmol, 1.00 equiv) and DTBMP (15.0 mg, 73.0 µmol, 4.44 equiv) and was then azeotropically dried with five portions of benzene. MeCN (3.5 mL) was introduced, and the resultant solution cooled to 0 °C. A solution of DMTSF (17.7 mg, 90.3 µmol, 5.48 equiv) in MeCN (200 µL) was then added dropwise via syringe to the stirred reaction mixture. The transfer was completed with two additional portions of MeCN (100 µL). After 30 min, the stirred reaction mixture was allowed to warm to ambient temperature before saturated aqueous $NaHCO_3$ solution (5 mL) was added. The mixture was partitioned with Et_2O (10 mL) and hexanes (10 mL) and the layers were separated. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 2% → 9% EtOAc in hexanes) to afford binaphthalene (+)-**129b**[144] (27.0 mg, 89%) as an orange film.**^{1}H NMR** (600 MHz, CD_2Cl_2) d: 14.84 (s, 1H), 14.16 (s, 1H), 9.49 (s, 1H), 7.46–7.35 (m, 13H), 7.32–7.27 (m, *J* = 5.1, 7.3 Hz, 2H), 7.11–7.04 (m, 8H), 7.02 (dd, *J* = 1.2, 7.8 Hz, 2H), 5.09 (d, *J* = 4.4 Hz, 1H), 5.08 (d, *J* = 4.4 Hz, 1H), 5.06–5.00 (m, 3H), 4.91 (d, *J* = 11.5 Hz, 2H), 4.80 (d, *J* = 10.6 Hz, 1H), 4.73 (d, *J* = 4.7 Hz, 1H), 4.71 (d, *J* = 4.7 Hz, 1H), 4.31–4.27 (m, 3H), 4.23 (d, *J* = 4.7 Hz, 1H), 3.96–3.92 (m, 4H), 3.90–3.88 (m, 4H), 3.83 (s, 3H), 3.58 (dt, *J* = 1.2, 15.4 Hz, 1H), 3.08 (dd, *J* = 13.4, 18.1 Hz, 1H), 2.54 (td, *J*

[144] Minor oxidation of (+)-**129b** occurs during purification and handling.

= 4.8, 13.9 Hz, 1H), 2.48 (td, *J* = 5.4, 13.2 Hz, 1H), 2.15 (ddd, *J* = 4.1, 12.5, 14.3 Hz, 1H), 2.04–1.97 (ddd, *J* = 4.1, 12.5, 14.6 Hz, 1H), 1.90 (ddd, *J* = 5.0, 12.1, 14.1 Hz, 1H), 1.83 (ddd, *J* = 4.8, 12.0, 14.3 Hz, 1H), 1.61–1.48 (m, 2H), 1.47–1.40 (m, 1H), 1.38–1.33 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.22 (s, 9H), 0.20 (s, 9H), 0.14 (s, 6H), 0.12 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.4, 204.3, 165.5, 157.6, 154.4, 153.2, 152.7, 152.4, 143.0, 142.5, 141.1, 139.6, 139.4, 139.2, 138.8, 138.6, 135.8, 135.7, 129.8, 129.6, 129.4, 128.7, 128.7, 128.5, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.7, 124.6, 123.4, 122.1, 120.5, 117.2, 116.2, 113.0, 112.9, 110.5, 110.2, 109.8, 87.9, 87.7, 87.0, 86.3, 83.6, 83.3, 82.0, 81.8, 77.8, 76.3, 76.1, 73.6, 73.4, 71.9, 71.7, 61.6, 61.3, 61.2, 49.5, 48.1, 40.8, 40.2, 28.5, 28.1, 28.0, 27.8, 27.6, 26.3, 26.3, 21.7, 18.6, 18.6, 18.3, 18.0, 15.3, 15.2, 2.4, 2.3, –4.0, –4.0, –4.2, –4.3.[145] **FTIR** (thin film) cm^{-1}: 3369, 2991, 1618, 1590, 1372, 1252, 1076, 1037, 842, 738, 698. **HRMS** (ESI) calc'd for $C_{110}H_{135}O_{21}Si_4$ $[M+H]^+$: 1831.8567, found 1831.8497. **$[\alpha]_D^{23}$**: +319 (*c* = 0.40, CH_2Cl_2). **TLC** (13% EtOAc in hexanes), R_f: 0.41 (UV, CAM).

[145] Due to the pseudo-C_2-symmetric nature of (+)-**129b** and the presence of multiple benzyl groups, one carbon resonance of a benzyl group of (+)-**129b** is unresolved as determined by comparison with related structures.



Nonacycle (–)-**130a**: A 10-mL round-bottom flask was charged with (–)-**129a** (27.0 mg, 14.7 μmol, 1.00 equiv) and was azeotropically dried with four portions of benzene. PhMe (3 mL) was introduced and the resultant solution was cooled to 0 °C. A solution of DDQ (12.5 mg, 55.1 μmol, 3.74 equiv) in PhMe (500 μL) was added dropwise via cannula to the stirred reaction mixture. The transfer was completed with two additional portions of PhMe (100 μL). After 3 h, a 1:1 mixture of 1% (w/v) aqueous $NaHSO_3$ solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture. The mixture was diluted with Et_2O (10 mL) and hexanes (10 mL), and the layers were separated. The combined organic layers were washed with a 1:1 mixture of 1% (w/v) aqueous $NaHSO_3$ solution and saturated aqueous $NaHCO_3$ solution (2 × 10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude naphthazarin **S13**, which was used without further purification.

A 100-mL round-bottom flask was charged with crude **S13** and azeotropically dried with five portions of benzene. 1,2-dichloroethane was then introduced (35 mL), and the resultant solution was cooled to 0 °C. A solution of anhydrous HCl in Et_2O (2.0 M, 370 μL, 740 μmol, 50 equiv) was added dropwise via syringe to the stirred solution. After 15 h, saturated aqueous $NaHCO_3$ solution (10 mL) was added to the stirred reaction mixture. The mixture was diluted with Et_2O (35 mL) and hexanes

(35 mL), and the layers were separated. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL), and brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% EtOAc in hexanes) to afford nonacycle (–)-**130a** (20.2 mg, 77% over two steps) as an orange film. **^{1}H NMR** (600 MHz, CD_2Cl_2) d: 14.92 (s, 1H), 13.76 (s, 1H), 9.58 (s, 1H), 7.49–7.42 (m, 9H), 7.38 (t, *J* = 7.7 Hz, 4H), 7.32–7.29 (m, 2H), 7.12–7.05 (m, 6H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 7.2 Hz, 2H), 5.89 (s, 1H), 5.12 (d, *J* = 10.6 Hz, 1H), 5.08–4.99 (m, 4H), 4.95–4.86 (m, 4H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.32 (d, *J* = 3.4 Hz, 1H), 4.28 (dd, *J* = 4.4, 8.7 Hz, 1H), 4.17 (dd, *J* = 3.7, 7.8 Hz, 1H), 4.10 (d, *J* = 7.8 Hz, 1H), 3.89 (dd, *J* = 3.4, 8.7 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78–3.74 (m, 4H), 3.62 (dd, *J* = 14.4, 15.3 Hz, 1H), 3.29 (dd, *J* = 5.2, 17.0 Hz, 1H), 2.50 (td, *J* = 5.0, 13.7 Hz, 1H), 2.44 (d, *J* = 3.7 Hz, 1H), 2.20 (ddd, *J* = 4.1, 12.0, 14.2 Hz, 1H), 1.89 (dt, *J* = 4.4, 13.3 Hz, 1H), 1.84–1.71 (m, 2H), 1.69–1.42 (m, 3H), 1.31 (s, 3H), 1.23–1.20 (m, 4H), 1.07 (dt, *J* = 3.6, 13.0 Hz, 1H), 0.95 (s, 9H), 0.94 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.25 (s, 9H), 0.18 (s, 9H), 0.13 (s, 3H), 0.11 (s, 6H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.4, 203.8, 165.5, 158.5, 154.6, 153.24, 153.17, 152.6, 143.8, 143.0, 140.05, 139.99, 139.4, 139.3, 138.6, 138.4, 135.8, 135.7, 129.9, 129.7, 129.5, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 125.3, 124.9, 122.6, 121.8, 118.7, 116.2, 113.0, 110.5, 109.9, 109.4, 88.1, 87.9, 87.8, 85.9, 85.1, 83.5, 82.2, 78.1, 76.5, 76.1, 75.5, 74.5, 73.2, 72.6, 71.8, 69.9, 61.7, 61.2, 61.2, 58.6, 49.5, 41.2, 35.8, 27.7, 27.6, 27.5, 26.3, 26.2, 18.6, 18.5, 18.4, 16.8, 15.3, 15.2, 2.3, 2.1, –4.0, –4.0, –4.1, –4.2.[146] **FTIR** (thin film) cm^{-1}: 3348, 2953, 1617, 1372, 1252, 1080, 842, 738, 698. **HRMS** (ESI) calc'd for $C_{101}H_{128}O_{21}NaSi_4$ $[M+Na]^+$: 1811.7917, found 1811.7824. **$[\alpha]_D^{23}$**: –195 (*c* = 0.40, CH_2Cl_2). **TLC** (17% EtOAc in hexanes), R_f: 0.42 (UV, CAM).

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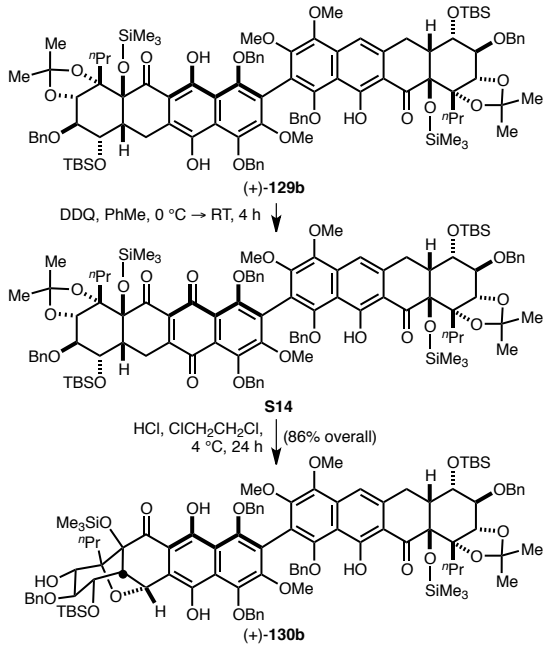
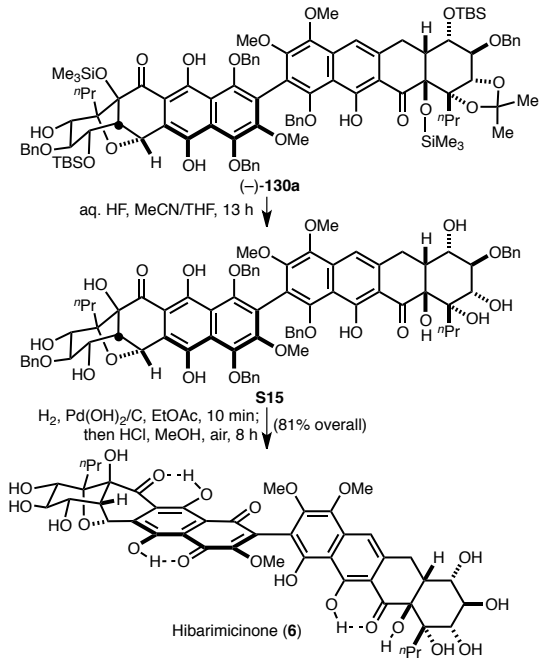
[146] Due to the pseudo-C_2-symmetric nature of (–)-**130a** and the presence of multiple benzyl groups, three carbon resonances of the benzyl group(s) of (–)-**130a** are unresolved as determined by comparison with related structures.



Nonacycle (+)-**130b**: A 25-mL round-bottom flask was charged with (+)-**129b** (21.1 mg, 11.5 μmol, 1.00 equiv) and was azeotropically dried with four portions of benzene. PhMe (2.5 mL) was introduced and the resultant solution was cooled to 0 °C. A solution of DDQ (10.0 mg, 44.0 μmol, 3.83 equiv) in PhMe (500 μL) was added dropwise via cannula to the stirred reaction mixture. The transfer was completed with two additional portions of PhMe (100 μL), and the stirred reaction was subsequently allowed to warm to ambient temperature. After 4 h, a 1:1 mixture of 1% (w/v) aqueous $NaHSO_3$ solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture. The mixture was diluted with Et_2O (10 mL) and hexanes (10 mL), and the layers were separated. The combined organic layers were washed with a 1:1 mixture of a 1% (w/v) aqueous $NaHSO_3$ solution and saturated aqueous $NaHCO_3$ solution (2 × 10 mL), saturated $NaHCO_3$ aqueous solution (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude naphthazarin **S14**, which was used immediately without further purification.

A 100-mL round-bottom flask was charged with crude **S14** and was azeotropically dried with four portions of benzene. 1,2-dichloroethane (25 mL) was then introduced, and the resultant solution was cooled to 4 °C. A solution of anhydrous HCl in Et_2O (2.0 M, 350 μL, 690 μmol, 60 equiv) was

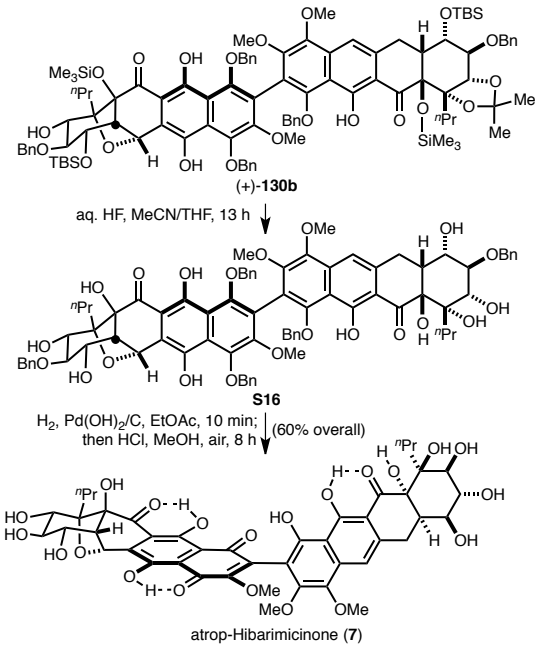
added dropwise via syringe to the stirred solution. After 25 h, saturated aqueous $NaHCO_3$ solution (10 mL) was added to the stirred reaction mixture. The mixture was diluted with Et_2O (25 mL) and hexanes (25 mL), and the layers were separated. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL), and brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 13% → 17% EtOAc in hexanes) to afford nonacycle (+)-**130b** (17.9 mg, 86% over two steps) as an orange film. **^{1}H NMR** (600 MHz, CD_2Cl_2) d: 14.84 (s, 1H), 13.73 (s, 1H), 9.55 (s, 1H), 7.49–7.40 (m, 10H), 7.37 (td, *J* = 7.5, 2.2 Hz 4H), 7.30 (t, *J* =7.5 Hz, 2H), 7.10–7.02 (m, 9H), 5.89 (s, 1H), 5.11 (d, *J* = 10.9 Hz, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 5.07–5.04 (m, 2H), 5.01 (d, *J* = 10.3 Hz, 1H), 4.95 (d, *J* = 13.7 Hz, 1H), 4.90 (d, *J* = 12.2 Hz, 1H), 4.88 (d, *J* = 12.2 Hz, 1H), 4.74 (d, *J* = 5.3 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.31–4.26 (m, 3H), 4.20 (dd, *J* = 3.8, 7.5 Hz, 1H), 4.09 (br. t, *J* = 6.2 Hz, 1H), 3.91 (s, 3H), 3.90–3.86 (m, 4H), 3.83 (s, 3H), 3.75 (t, *J* = 7.7 Hz, 1H), 3.59 (t, *J* = 15.3 Hz, 1H), 3.29 (dd, *J* = 5.3, 17.2 Hz, 1H), 2.53 (td, *J* = 5.0, 13.8 Hz, 1H), 2.50 (d, *J* = 3.7 Hz, 1H), 2.15 (ddd, *J* = 3.9, 12.1, 14.3 Hz, 1H), 1.88–1.79 (m, 2H), 1.76 (br. d, *J* = 7.2 Hz, 1H), 1.67–1.51 (m, 2H), 1.49–1.37 (m, 1H), 1.31 (s, 3H), 1.24–1.18 (m, 4H), 1.04–0.98 (m, 10H), 0.97 (s, 9H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H), 0.27 (s, 9H), 0.19 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ: 204.4, 203.7, 165.4, 158.5, 154.6, 153.3, 153.2, 152.5, 143.8, 143.1, 140.0, 139.9, 139.4, 139.3, 138.9, 138.5, 135.8, 135.6, 130.0, 129.8, 129.5, 128.8, 128.7, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.5, 127.3, 125.2, 125.0, 122.5, 121.9, 118.7, 116.1, 112.9, 110.6, 109.8, 109.8, 88.1, 87.9, 87.9, 86.3, 85.1, 83.3, 82.1, 78.1, 76.4, 76.1, 75.5, 74.5, 73.4, 72.6, 71.7, 69.9, 61.8, 61.3, 61.1, 58.6, 49.5, 40.8, 35.8, 28.1, 27.8, 27.7, 26.3, 26.2, 18.6, 18.5, 18.3, 16.8, 15.3, 15.2, 2.3, 2.1, –4.0, –4.0, –4.0, –4.2. **FTIR** (thin film) cm^{-1}: 3356, 2953, 1653, 1373, 1252, 1081, 844, 737, 697. **HRMS** (ESI) calc'd for $C_{101}H_{129}O_{21}Si_4$ $[M+H]^+$: 1789.8098, found 1789.8146. **$[\alpha]_D^{23}$**: +233 (*c* = 0.40, CH_2Cl_2). **TLC** (17% EtOAc in hexanes), R_f: 0.21 (UV, CAM).



Hibarimicinone (6): Concentrated aqueous HF solution (48 wt. %, 3 mL) was slowly added to a stirred solution of (–)-**130a** (11.5 mg, 6.40 μmol, 1.00 equiv) in 1:1 MeCN/THF (6 mL) in a polyethylene vessel at ambient temperature. After 13 h, the reaction mixture was cautiously poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ solution (50 mL), Et_2O (30 mL), and ice at 0 °C. After gas evolution ceased, the stirred mixture was diluted with EtOAc (50 mL) and the layers were separated. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then quickly passed through a plug of silica gel (eluent: gradient, 20% → 50% EtOAc in hexanes) to afford crude nonacycle **S15** as an orange film, which was used without further purification.

A 25-mL round-bottom flask was charged with crude **S15** and EtOAc (8.5 mL). Palladium hydroxide on carbon (20 wt. % loading (dry basis), 88.0 mg, 125 μmol, 19.6 equiv) was added in a single portion to the stirred solution, which was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen gas for an additional 5 min before the balloon was removed. After an additional 10 min, the hydrogen balloon was removed and

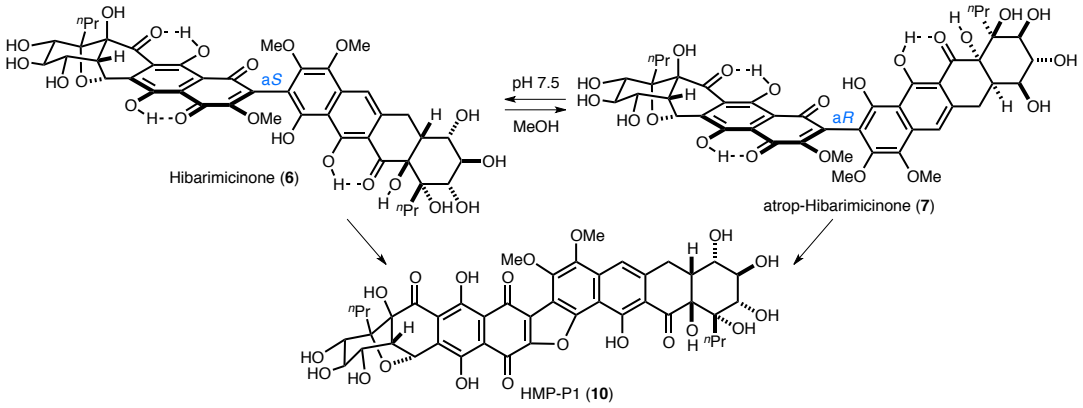
the stirred reaction mixture was sparged with argon gas. After 2 min, a solution of HCl in MeOH (1.5 M, 8.5 mL) was rapidly added via syringe to the stirred reaction mixture, which was then immediately filtered through a 0.2 μm PVDF syringe filter to give an orange-yellow homogeneous solution. The resultant orange-yellow solution was stirred under ambient atmosphere and turned red over time. After 8 h, the solution was partitioned with EtOAc (50 mL) and brine (25 mL), and the layers were separated. The organic layer was washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant maroon film was purified by semi-preparatory HPLC on a Cosmosil 5C18-AR-II column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: aqueous 0.15% (v/v) KH_2PO_4 pH 3.5 buffer, isocratic elution with 60% A for 20 min, flow rate: 4.0 mL/min]. Fractions eluting at 10–13 min were collected and washed with hexanes (5 × 100 mL) and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with brine (3 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford hibarimicinone (**6**) (4.8 mg, 81%) as a dark maroon film. **^{1}H NMR** (600 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1) d: 7.35 (s, 1H), 5.83 (s, 1H), 4.10–4.05 (m, 2H), 3.98 (d, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.96–3.92 (m, 1H), 3.85 (s, 3H), 3.80 (t, *J* = 8.5 Hz, 1H), 3.73 (d, *J* = 9.4 Hz, 1H), 3.75–3.69 (m, 1H), 3.18 (dd, *J* = 6.0, 17.1 Hz, 1H), 2.65 (td, *J* = 5.6, 13.3 Hz, 1H), 2.57 (d, *J* = 3.8 Hz, 1H), 1.88 (dt, *J* = 4.2, 13.4 Hz, 1H), 1.81 (dt, *J* = 4.2, 13.4 Hz, 1H), 1.77–1.65 (m, 2H), 1.51–1.41 (m, 1H), 1.39–1.30 (m, 1H), 1.26–1.18 (m, 1H), 1.01 (dt, *J* = 4.2, 13.4 Hz, 1H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1) δ: 207.4, 198.4, 189.1, 186.3, 165.4, 160.0, 158.0, 154.2, 153.3, 151.9, 149.4, 142.1, 139.7, 136.3, 127.5, 126.7, 117.7, 114.3, 112.6, 112.3, 109.7, 109.2, 87.6, 84.9, 80.7, 80.1, 79.2, 76.0, 75.1, 74.1, 71.6, 71.3, 69.1, 61.7, 61.7, 61.6, 58.7, 48.1, 39.0, 36.1, 28.6, 19.3, 17.6, 15.7, 15.3. **FTIR** (thin film) cm^{-1}: 3389, 2944, 1692, 1625, 1412, 1188, 1032. **HRMS** (ESI) calc'd for $C_{45}H_{49}O_{21}$ $[M+H]^+$: 925.2761, found 925.2747. **TLC** (silica gel RP-18, 45% water in MeCN), R_f: 0.55 (UV).



atrop-Hibarimicinone (**7**): Concentrated aqueous HF solution (48 wt. %, 3 mL) was slowly added to a stirred solution of (–)-**130b** (9.7 mg, 5.4 μmol, 1.0 equiv) in 1:1 MeCN/THF (6 mL) in a polyethylene vessel at ambient temperature. After 13 h, the reaction mixture was cautiously poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ solution (50 mL), Et_2O (30 mL), and ice at 0 °C. After gas evolution ceased, the stirred mixture was diluted with EtOAc (50 mL) and the layers were separated. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then quickly passed through a plug of silica gel (eluent: gradient, 20% → 50% EtOAc in hexanes) to afford crude nonacycle **S16** as an orange film, which was used without further purification.

A 25-mL round-bottom flask was charged with crude **S16** and EtOAc (7 mL). Palladium hydroxide on carbon (20 wt. % loading (dry basis), 75.0 mg, 105 μmol, 19.3 equiv) was added in a single portion to the stirred solution, which was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen gas for an additional 5 min before the balloon was removed. After an additional 10 min, the hydrogen balloon was removed and

the stirred reaction mixture was sparged with argon gas. After 2 min, a solution of HCl in MeOH (1.5 M, 7 mL) was rapidly added via syringe to the stirred reaction mixture, which was then immediately filtered through a 0.2 μm PVDF syringe filter to give an orange-yellow homogeneous solution. The resultant orange-yellow solution was stirred under ambient atmosphere and turned red over time. After 8 h, the solution was partitioned with EtOAc (50 mL) and brine (25 mL), and the layers were separated. The organic layer was washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant maroon film was purified by semi-preparatory HPLC on a Cosmosil 5C18-AR-II column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: aqueous 0.15% (v/v) KH_2PO_4 pH 3.5 buffer, isocratic elution with 60% A for 20 min, flow rate: 3.5 mL/min]. Fractions eluting at 10–13 min were collected and washed with hexanes (5 × 100 mL) and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with brine (3 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford atrop-hibarimicinone (**7**) (3.0 mg, 60%) as a dark maroon film. **^{1}H NMR** (600 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1) d: 7.35 (s, 1H), 5.84 (s, 1H), 4.11–4.06 (m, 2H), 3.99 (d, *J* = 7.9 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.95–3.91 (m, 1 H), 3.85 (s, 3H), 3.80 (t, *J* = 8.2 Hz, 1H), 3.74 (d, *J* = 9.4 Hz, 1H), 3.76–3.68 (m, 1H), 2.66 (td, *J* = 5.7, 13.4 Hz, 1H), 2.58 (d, *J* = 3.5 Hz, 1H), 1.89 (dt, *J* = 4.1, 13.8 Hz, 1H), 1.80 (dt, *J* = 4.4, 13.5 Hz, 3 H), 1.77–1.66 (m, 2H), 1.53–1.43 (m, 1H), 1.39–1.30 (m, 1H), 1.28–1.19 (m, 1H), 1.00 (dt, *J* = 4.5, 13.3 Hz, 1H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1) δ: 207.4, 198.4, 189.2, 186.2, 165.3, 160.0, 157.9, 154.3, 153.2, 151.9, 149.4, 142.1, 139.8, 136.2, 127.2, 126.7, 117.6, 114.3, 112.6, 112.3, 109.7, 109.3, 87.6, 84.9, 80.7, 80.0, 79.2, 76.0, 75.1, 74.1, 71.7, 71.3, 69.1, 61.7, 61.7, 61.6, 58.7, 48.0, 39.0, 36.2, 28.6, 19.3, 17.6, 15.7, 15.3. **FTIR** (thin film) cm^{-1}: 3489, 2956, 1694, 1625, 1408, 1200, 1057. **HRMS** (ESI) calc'd for $C_{45}H_{49}O_{21}$ $[M+H]^+$: 925.2761, found 925.2745. **TLC** (silica gel RP-18, 45% water in MeCN), R_f: 0.55 (UV).



HMP-P1 (10), and Hibarimicinone (6) and atrop-hibarimicinone (7) isomerization studies:

From **6**: To a stirred solution of **6** (3.2 mg, 3.5 µmol, 1.0 equiv) in MeOH (5 mL) was added an aqueous NaH_2PO_4/NaOH pH 7.5 buffered solution (0.20 M, 25 µL). The progress of the reaction was monitored by HPLC analysis of small aliquots on a Cosmosil 5C18-AR-II column [5 µm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: 0.05% (v/v) trifluoroacetic acid in water, injection volume 200 µL (methanol/10% (v/v) HCl in water), isocratic elution with 60% A for 25 min, flow rate: 3.0 mL/min]. See Appendix C Figure S6 for HPLC traces. During this time, the reaction color changes from brownish red to indigo. After 27 h, the reaction mixture was acidified with a solution of HCl in MeOH (1.5 N, 100 µL), whereupon the reaction turns purple. The reaction mixture was then concentrated under reduced pressure. The residue was then purified by semi-preparatory HPLC on a Cosmosil 5C18-AR-II column [5 µm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: 0.05% (v/v) trifluoroacetic acid in water, isocratic elution with 60% A for 25 min, flow rate: 3.5 mL/min]. Fractions eluting at 17–21 min were collected and concentrated under reduced pressure to afford HMP-P1 (**10**) (2.6 mg, 84%) as a dark purple film.

From **7**: To a stirred solution of **7** (2.7 mg, 3.5 µmol, 1.0 equiv) in MeOH (5 mL) was added an aqueous NaH_2PO_4/NaOH pH 7.5 buffered solution (0.20 M, 25 µL). The progress of the reaction was monitored by HPLC analysis of small aliquots on a Cosmosil 5C18-AR-II column [5 µm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B:

0.05% (v/v) trifluoroacetic acid in water, injection volume 200 μL (methanol/10% (v/v) HCl in water), isocratic elution with 60% A for 25 min, flow rate: 3.0 mL/min]. See Appendix C Figure S7 for HPLC traces. During this time, the reaction color changes from brownish red to indigo. After 27 h, the reaction mixture was acidified with a solution of HCl in MeOH (1.5 N, 100 μL), whereupon the reaction turns purple. The reaction mixture was then concentrated under reduced pressure. The residue was then purified by semi-preparatory HPLC on a Cosmosil 5C18-AR-II column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: 0.05% (v/v) trifluoroacetic acid in water, isocratic elution with 60% A for 25 min, flow rate: 3.5 mL/min]. Fractions eluting at 17–21 min were collected and concentrated under reduced pressure to afford HMP-P1 (**10**) (2.2 mg, 84%) as a dark purple film.

2-mL vials were charged with either a dilute solution of **6** or **7** in acidic methanol (1.0 M) and were heated to 60 °C for 90 minutes. The solutions were then cooled to room temperature and analyzed by HPLC analysis on a Cosmosil 5C18-AR-II column [5 μm, 10.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: MeOH, solvent B: 0.05% (v/v) trifluoroacetic acid in water, injection volume 200 μL (methanol/10% (v/v) HCl in water), isocratic elution with 60% A for 25 min, flow rate: 3.0 mL/min]. See Appendix C Figure S8–S11 for HPLC traces. **^{1}H NMR** (600 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1) d: 7.30 (s, 1H), 5.87 (s, 1H), 4.20 (dd, *J* = 3.7, 8.3 Hz, 1H), 4.11 (dd, *J* = 5.9, 10.0 Hz, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 4.02 (d, *J* = 7.9 Hz, 1H), 3.93 (t, *J* = 9.5 Hz, 1H), 3.85 (t, *J* = 7.9 Hz, 1H), 3.71 (d, *J* = 9.1 Hz, 1H), 3.67 (dd, *J* = 14.4, 17.6 Hz, 1H), 3.17 (dd, *J* = 5.3, 17.0 Hz, 1H), 2.94 (d, *J* = 3.8 Hz, 1H), 2.68 (td, *J* = 5.8, 13.0 Hz, 1H), 1.87 (dt, *J* = 3.5, 13.3 Hz, 1H), 1.75–1.64 (m, 2H), 1.63–1.55 (m, 1H), 1.50–1.39 (m, 1H), 1.33–1.18 (m, 2H), 0.98 (dt, *J* = 3.8, 13.2 Hz, 1H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 207.7, 196.8, 183.0, 177.1, 160.7, 157.7, 152.2, 151.0, 150.3, 148.9, 146.9, 144.9, 144.4, 134.3, 125.6, 125.5, 116.9, 115.8, 114.5, 113.8, 111.4, 107.2, 86.1, 83.4, 79.3, 78.5, 77.3, 73.8, 72.8, 72.2, 69.5, 69.5, 66.9, 62.2, 61.6, 57.1, 46.4, 37.5, 34.9, 28.2, 17.7, 15.8, 15.3, 14.9. **FTIR** (thin film) cm^{-1}: 3421, 2925, 1697, 1633, 1458, 1415, 1123, 1031. **HRMS** (ESI) calc'd

for $C_{44}H_{45}O_{21}$ $[M+H]^+$: 893.2499, found 823.2485. **TLC** (silica gel RP-18, 45% water in MeCN), R_f: 0.60 (UV).

Appendix A

Chapter Two Supplementary Figures

Table S1. ^{13}C NMR data comparison between reported natural and synthetic (+)-fastigiatine (**37**).

Literature Report[147] (^{13}C, 101 MHz, $CDCl_3$)	This Report (^{13}C, 126 MHz, $CDCl_3$)
21.1	21.3
21.5	21.7
22.3	22.5
23.0	23.1
25.5	25.7
33.9	34.0
34.6	34.7
35.0	35.2
37.4	37.5
38.3	38.5
40.2	40.3
45.3	45.5
45.5	45.6
55.0	55.2
59.6	59.8
65.4	65.6
123.1	123.3
139.2	139.3
170.0	170.2

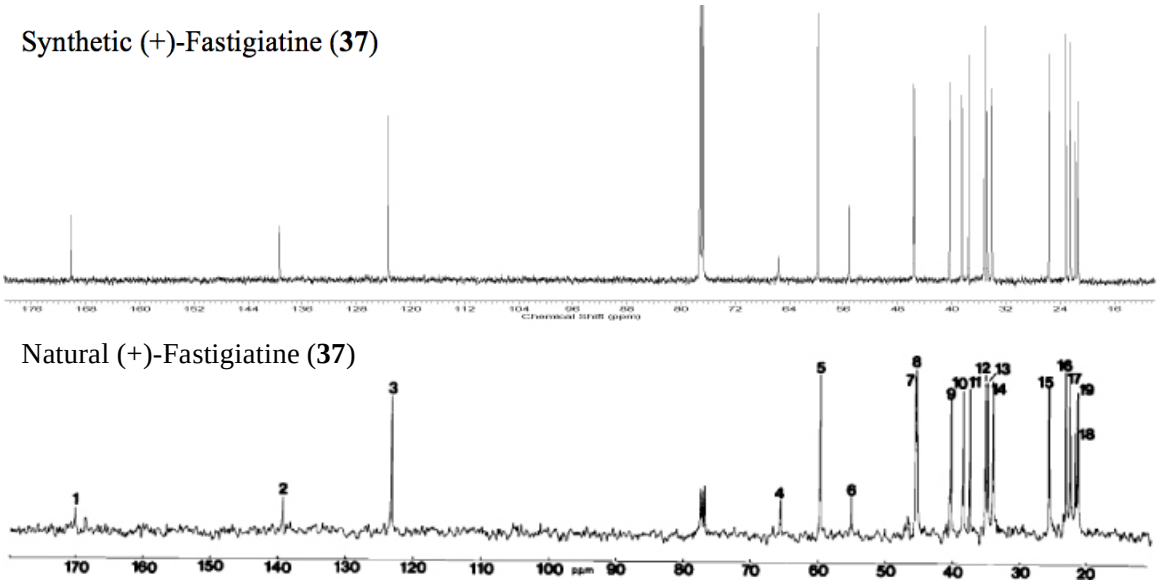


Figure S1. Comparison of ^{13}C NMR spectra of natural and synthetic (+)-fastigiatine (**37**).

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[147] Gerard, R. V.; MacLean, D. B.; Fagianni, R.; Lock, C. J. *Can. J. Chem.* **1986**, *64*, 943–949. Tabulated ^{1}H NMR data was not provided.

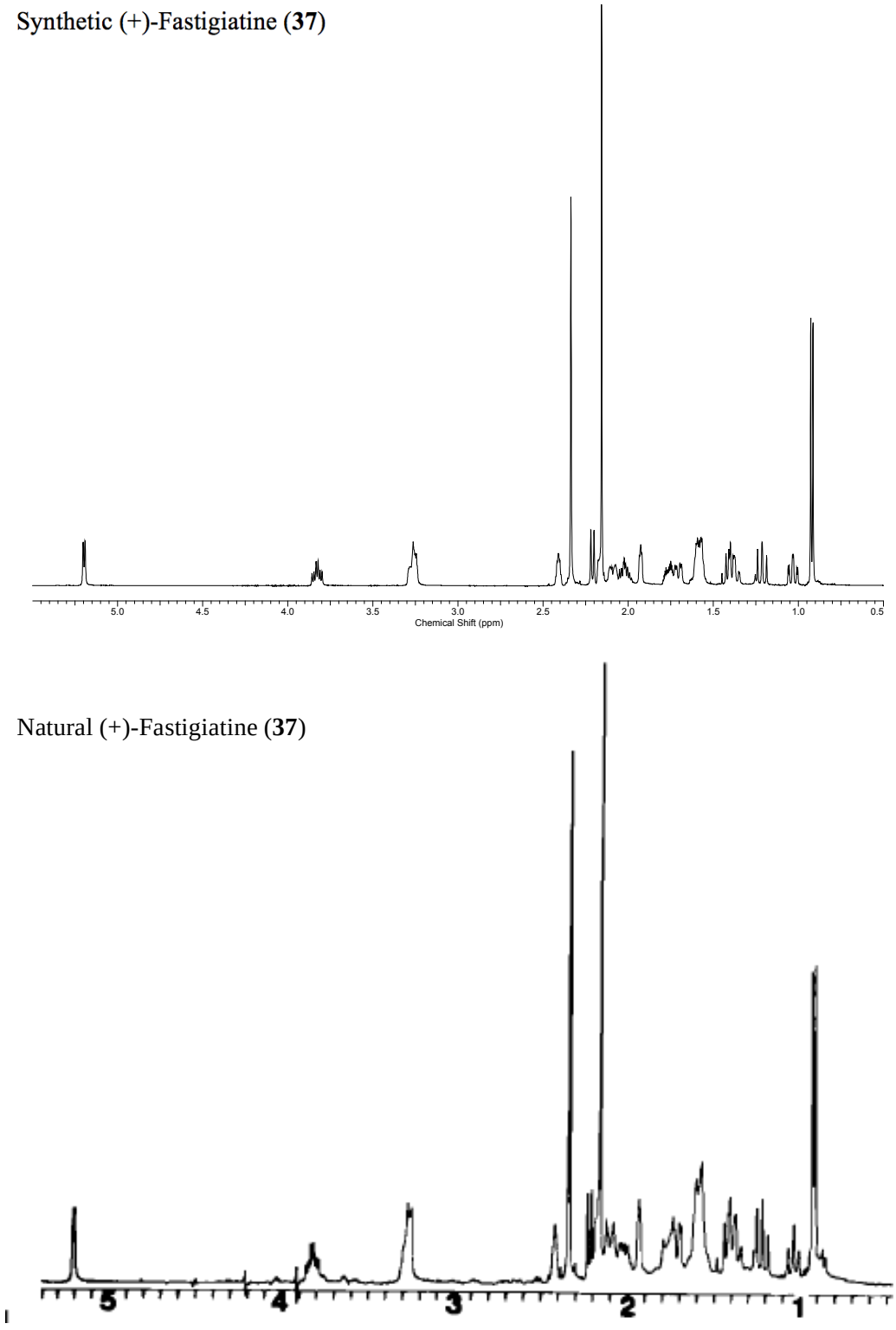
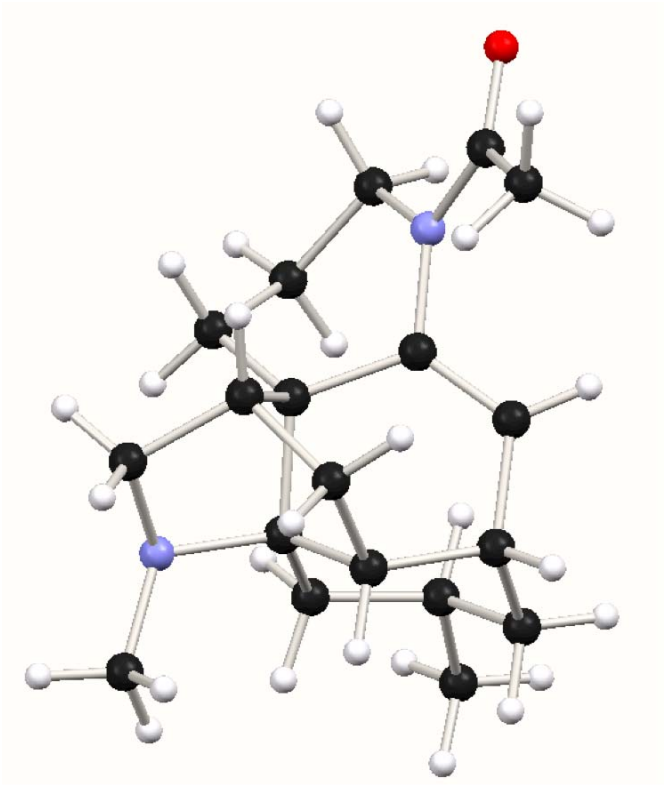


Figure S2. Comparison of ^{1}H NMR spectra of natural and synthetic (+)-fastigiatine (**37**).

View 1:



View 2:

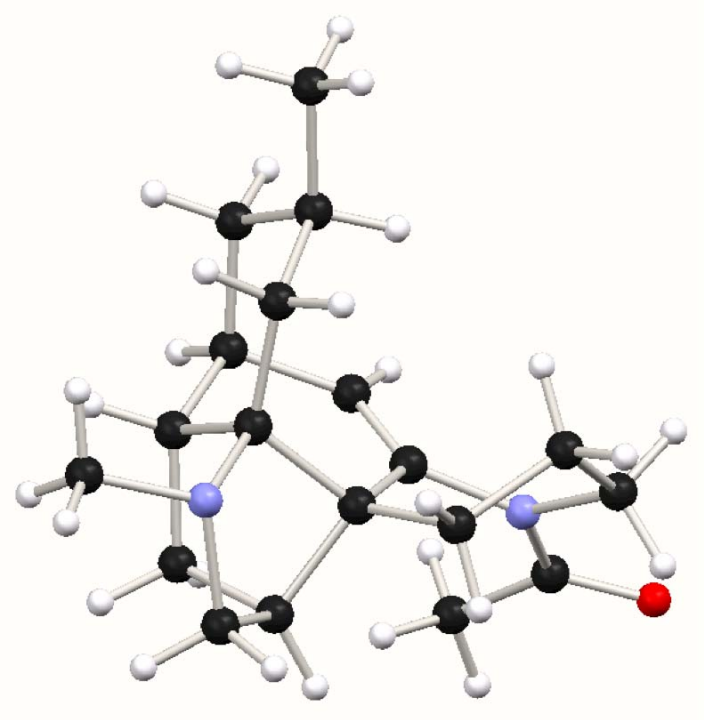


Figure S3. X-Ray crystal structure of (+)-fastigiatine (**37**).

X-Ray Crystallography. A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.78 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table S2. Experimental details.

Crystal data	
Chemical formula	$C_{19}H_{28}N_2O$
M_r	300.43
Crystal system, space group	ORTHORHOMBIC, $P2_12_12_1$
Temperature (K)	100
a, *b*, *c* (Å)	8.3421 (5), 8.7999 (5), 22.1725 (12)
V (Å^3)	1627.68 (16)
Z	4
Radiation type	Mo *K*a
m (mm^{-1})	0.08
Crystal size (mm)	0.38 × 0.24 × 0.08
Data collection	
Diffractometer	CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.972, 0.994
No. of measured, independent and observed [$I > 2s(I)$] reflections	47047, 3894, 3780
R_{int}	0.041
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.036, 0.094, 1.06
No. of reflections	3894
No. of parameters	202
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$D\rho_{max}$, $D\rho_{min}$ (e Å^{-3})	0.38, -0.16
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	-1.1 (11)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL*.

Table S3. Selected geometric parameters (Å, º)

O1—C17	1.2306 (14)	C9—C14	1.5370 (16)
N1—C16	1.4613 (15)	C9—C10	1.5426 (16)
N1—C1	1.4906 (15)	C9—H9	1.0000
N1—C13	1.4919 (14)	C10—C11	1.5357 (16)
N2—C17	1.3655 (14)	C10—H10A	0.9900
N2—C7	1.4298 (14)	C10—H10B	0.9900
N2—C6	1.4759 (14)	C11—C19	1.5290 (15)
C1—C2	1.5213 (16)	C11—C12	1.5323 (16)
C1—H1B	0.9900	C11—H11	1.0000
C1—H1A	0.9900	C12—C13	1.5260 (14)
C2—C15	1.5520 (16)	C12—H12A	0.9900
C2—C3	1.5567 (15)	C12—H12B	0.9900
C2—H2	1.0000	C13—C14	1.5481 (15)
C3—C7	1.5184 (15)	C14—C15	1.5564 (15)
C3—C4	1.5433 (15)	C14—H14	1.0000
C3—C13	1.5593 (15)	C15—H15B	0.9900
C4—C5	1.5291 (16)	C15—H15A	0.9900
C4—H4B	0.9900	C16—H16A	0.9800
C4—H4A	0.9900	C16—H16B	0.9800
C5—C6	1.5234 (15)	C16—H16C	0.9800
C5—H5B	0.9900	C17—C18	1.5104 (16)
C5—H5A	0.9900	C18—H18A	0.9800
C6—H6B	0.9900	C18—H18C	0.9800
C6—H6A	0.9900	C18—H18B	0.9800
C7—C8	1.3348 (15)	C19—H19A	0.9800
C8—C9	1.5109 (16)	C19—H19B	0.9800
C8—H8	0.9500	C19—H19C	0.9800
C16—N1—C1	112.32 (9)	C9—C10—H10A	109.3
C16—N1—C13	116.88 (9)	C11—C10—H10B	109.3
C1—N1—C13	106.28 (8)	C9—C10—H10B	109.3
C17—N2—C7	124.84 (9)	H10A—C10—H10B	108.0
C17—N2—C6	117.62 (9)	C19—C11—C12	109.98 (10)
C7—N2—C6	117.55 (9)	C19—C11—C10	111.36 (9)

Table S3. (continued)			
N1—C1—C2	103.02 (9)	C12—C11—C10	111.12 (10)
N1—C1—H1B	111.2	C19—C11—H11	108.1
C2—C1—H1B	111.2	C12—C11—H11	108.1
N1—C1—H1A	111.2	C10—C11—H11	108.1
C2—C1—H1A	111.2	C13—C12—C11	115.78 (9)
H1B—C1—H1A	109.1	C13—C12—H12A	108.3
C1—C2—C15	107.09 (10)	C11—C12—H12A	108.3
C1—C2—C3	100.70 (9)	C13—C12—H12B	108.3
C15—C2—C3	102.40 (9)	C11—C12—H12B	108.3
C1—C2—H2	115.0	H12A—C12—H12B	107.4
C15—C2—H2	115.0	N1—C13—C12	110.05 (9)
C3—C2—H2	115.0	N1—C13—C14	112.07 (9)
C7—C3—C4	110.15 (9)	C12—C13—C14	113.58 (9)
C7—C3—C2	110.56 (9)	N1—C13—C3	100.68 (8)
C4—C3—C2	114.56 (9)	C12—C13—C3	119.95 (9)
C7—C3—C13	112.99 (9)	C14—C13—C3	99.58 (8)
C4—C3—C13	115.01 (9)	C9—C14—C13	108.08 (9)
C2—C3—C13	92.58 (8)	C9—C14—C15	113.09 (9)
C5—C4—C3	110.57 (9)	C13—C14—C15	102.04 (9)
C5—C4—H4B	109.5	C9—C14—H14	111.1
C3—C4—H4B	109.5	C13—C14—H14	111.1
C5—C4—H4A	109.5	C15—C14—H14	111.1
C3—C4—H4A	109.5	C2—C15—C14	103.42 (9)
H4B—C4—H4A	108.1	C2—C15—H15B	111.1
C6—C5—C4	110.27 (9)	C14—C15—H15B	111.1
C6—C5—H5B	109.6	C2—C15—H15A	111.1
C4—C5—H5B	109.6	C14—C15—H15A	111.1
C6—C5—H5A	109.6	H15B—C15—H15A	109.0
C4—C5—H5A	109.6	N1—C16—H16A	109.5
H5B—C5—H5A	108.1	N1—C16—H16B	109.5
N2—C6—C5	109.59 (9)	H16A—C16—H16B	109.5
N2—C6—H6B	109.8	N1—C16—H16C	109.5
C5—C6—H6B	109.8	H16A—C16—H16C	109.5
N2—C6—H6A	109.8	H16B—C16—H16C	109.5

Table S3. (continued)			
C5—C6—H6A	109.8	O1—C17—N2	120.14 (10)
H6B—C6—H6A	108.2	O1—C17—C18	120.89 (10)
C8—C7—N2	122.02 (10)	N2—C17—C18	118.90 (10)
C8—C7—C3	123.25 (10)	C17—C18—H18A	109.5
N2—C7—C3	114.71 (9)	C17—C18—H18C	109.5
C7—C8—C9	120.25 (10)	H18A—C18—H18C	109.5
C7—C8—H8	119.9	C17—C18—H18B	109.5
C9—C8—H8	119.9	H18A—C18—H18B	109.5
C8—C9—C14	109.54 (9)	H18C—C18—H18B	109.5
C8—C9—C10	109.91 (10)	C11—C19—H19A	109.5
C14—C9—C10	110.07 (9)	C11—C19—H19B	109.5
C8—C9—H9	109.1	H19A—C19—H19B	109.5
C14—C9—H9	109.1	C11—C19—H19C	109.5
C10—C9—H9	109.1	H19A—C19—H19C	109.5
C11—C10—C9	111.48 (9)	H19B—C19—H19C	109.5
C11—C10—H10A	109.3		
C16—N1—C1—C2	127.40 (10)	C16—N1—C13—C12	71.61 (12)
C13—N1—C1—C2	-1.59 (11)	C1—N1—C13—C12	-162.12 (9)
N1—C1—C2—C15	-69.42 (11)	C16—N1—C13—C14	-55.80 (13)
N1—C1—C2—C3	37.25 (10)	C1—N1—C13—C14	70.47 (11)
C1—C2—C3—C7	-171.62 (9)	C16—N1—C13—C3	-160.82 (10)
C15—C2—C3—C7	-61.26 (11)	C1—N1—C13—C3	-34.55 (10)
C1—C2—C3—C4	63.21 (11)	C11—C12—C13—N1	-173.19 (9)
C15—C2—C3—C4	173.57 (9)	C11—C12—C13—C14	-46.63 (13)
C1—C2—C3—C13	-55.86 (9)	C11—C12—C13—C3	70.83 (13)
C15—C2—C3—C13	54.49 (10)	C7—C3—C13—N1	168.23 (8)
C7—C3—C4—C5	24.71 (12)	C4—C3—C13—N1	-64.11 (11)
C2—C3—C4—C5	150.10 (9)	C2—C3—C13—N1	54.59 (9)
C13—C3—C4—C5	-104.36 (11)	C7—C3—C13—C12	-71.02 (12)
C3—C4—C5—C6	-65.30 (12)	C4—C3—C13—C12	56.64 (13)
C17—N2—C6—C5	-165.71 (10)	C2—C3—C13—C12	175.34 (10)
C7—N2—C6—C5	14.43 (13)	C7—C3—C13—C14	53.43 (11)
C4—C5—C6—N2	44.39 (12)	C4—C3—C13—C14	-178.91 (9)
C17—N2—C7—C8	-54.47 (16)	C2—C3—C13—C14	-60.21 (9)

Table S3. (continued)			
C6—N2—C7—C8	125.37 (12)	C8—C9—C14—C13	59.78 (11)
C17—N2—C7—C3	123.82 (11)	C10—C9—C14—C13	-61.18 (11)
C6—N2—C7—C3	-56.34 (13)	C8—C9—C14—C15	-52.42 (12)
C4—C3—C7—C8	-148.97 (10)	C10—C9—C14—C15	-173.38 (9)
C2—C3—C7—C8	83.40 (13)	N1—C13—C14—C9	178.98 (9)
C13—C3—C7—C8	-18.81 (15)	C12—C13—C14—C9	53.49 (12)
C4—C3—C7—N2	32.76 (12)	C3—C13—C14—C9	-75.29 (10)
C2—C3—C7—N2	-94.87 (10)	N1—C13—C14—C15	-61.58 (11)
C13—C3—C7—N2	162.92 (9)	C12—C13—C14—C15	172.92 (9)
N2—C7—C8—C9	177.43 (10)	C3—C13—C14—C15	44.15 (10)
C3—C7—C8—C9	-0.71 (16)	C1—C2—C15—C14	76.37 (11)
C7—C8—C9—C14	-19.20 (14)	C3—C2—C15—C14	-29.09 (11)
C7—C8—C9—C10	101.86 (12)	C9—C14—C15—C2	106.68 (10)
C8—C9—C10—C11	-58.49 (13)	C13—C14—C15—C2	-9.16 (11)
C14—C9—C10—C11	62.25 (12)	C7—N2—C17—O1	172.09 (10)
C9—C10—C11—C19	-174.81 (10)	C6—N2—C17—O1	-7.76 (15)
C9—C10—C11—C12	-51.83 (13)	C7—N2—C17—C18	-11.01 (16)
C19—C11—C12—C13	168.35 (10)	C6—N2—C17—C18	169.14 (10)
C10—C11—C12—C13	44.58 (13)		

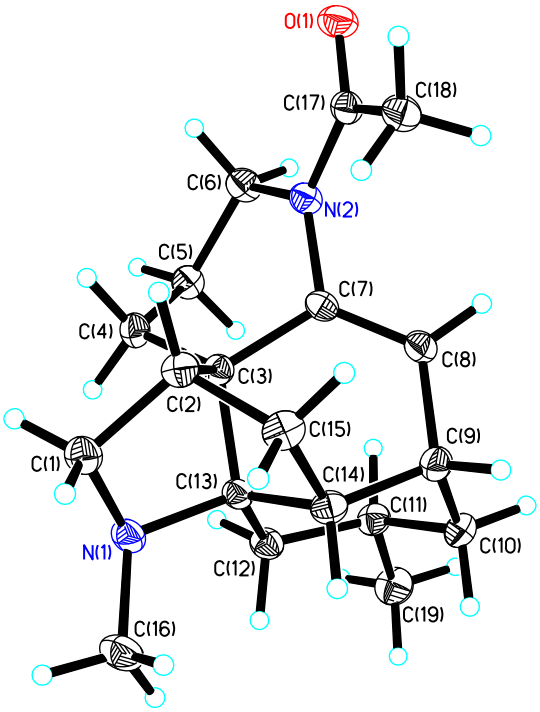


Figure S4. Perspective views showing 50%.

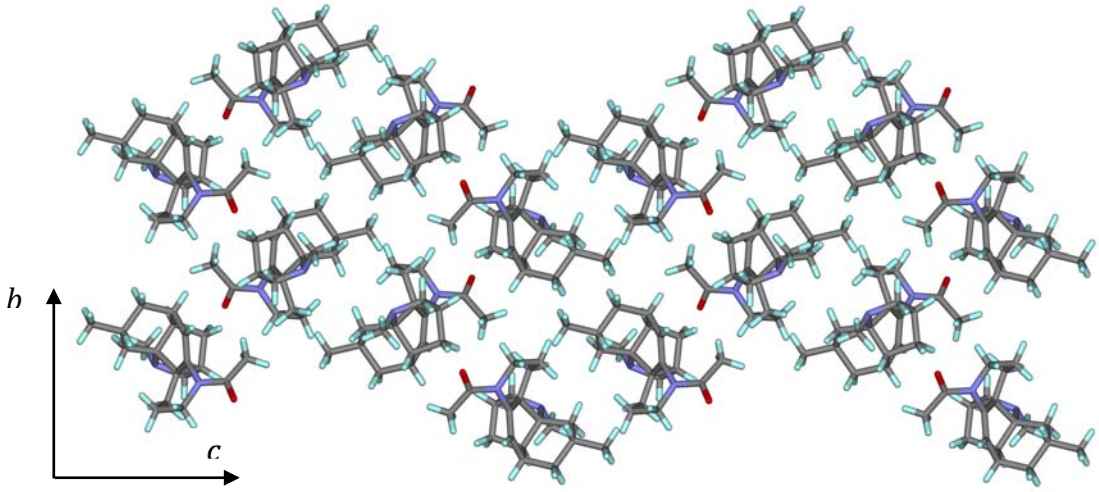
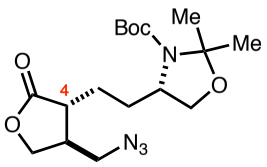


Figure S5. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

Appendix B

Chapter Two Catalog of ^{1}H and ^{13}C NMR Spectra



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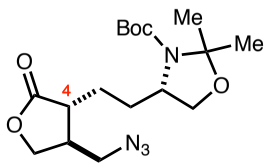

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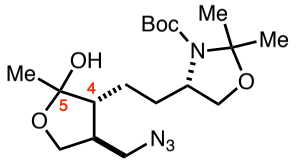

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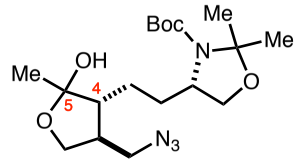
complex mixture of diastereomers



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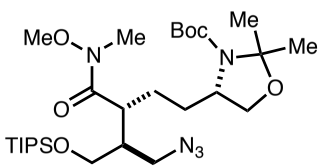
complex mixture of diastereomers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N
Me
Boc
N
Me
Me
O
O
TIPSO
N3

S4

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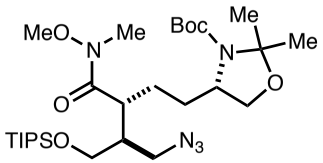
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)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N
Me
Boc
N
Me
Me
O
O
TIPSO
N3

S4

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200
190
180
170
160
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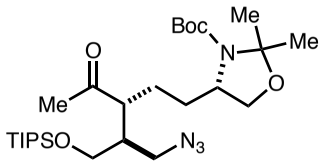
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)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N
Me
O
O
Me
TIPSO
N_3

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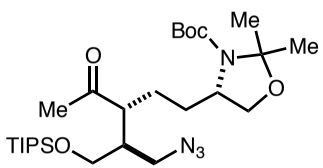
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Me
N
Me
O
O
Me
TIPSO
N_3

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210
200
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170
160
150
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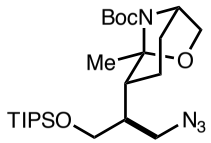
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



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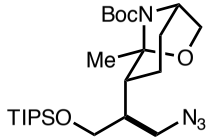
BocN
Me
O
TIPSO
N_3

76

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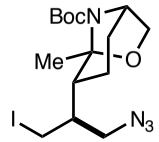
40
30
20
10
0
-10
Chemical Shift (ppm)



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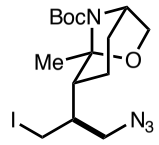
BocN
Me
O
I
N3

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200
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180
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160
150
140
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110
100
90
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70
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50
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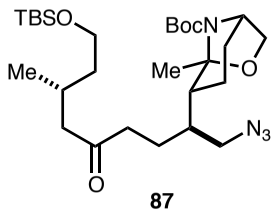
30
20
10
0
-10
Chemical Shift (ppm)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BocN
Me
Me
O
N3
O

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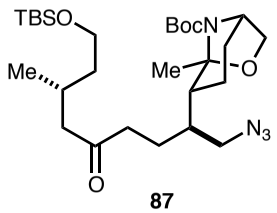
2.0
1.0
0
Chemical Shift (ppm)


TBSO
BocN
Me
Me
O
N3
O

87

210
200
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180
170
160
150
140
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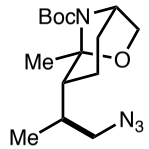
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



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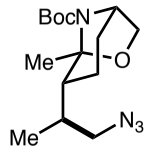
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Me
N_3

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200
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170
160
150
140
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30
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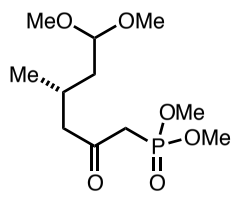
0
-10
Chemical Shift (ppm)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OMe
Me
OMe
P
OMe
O
O

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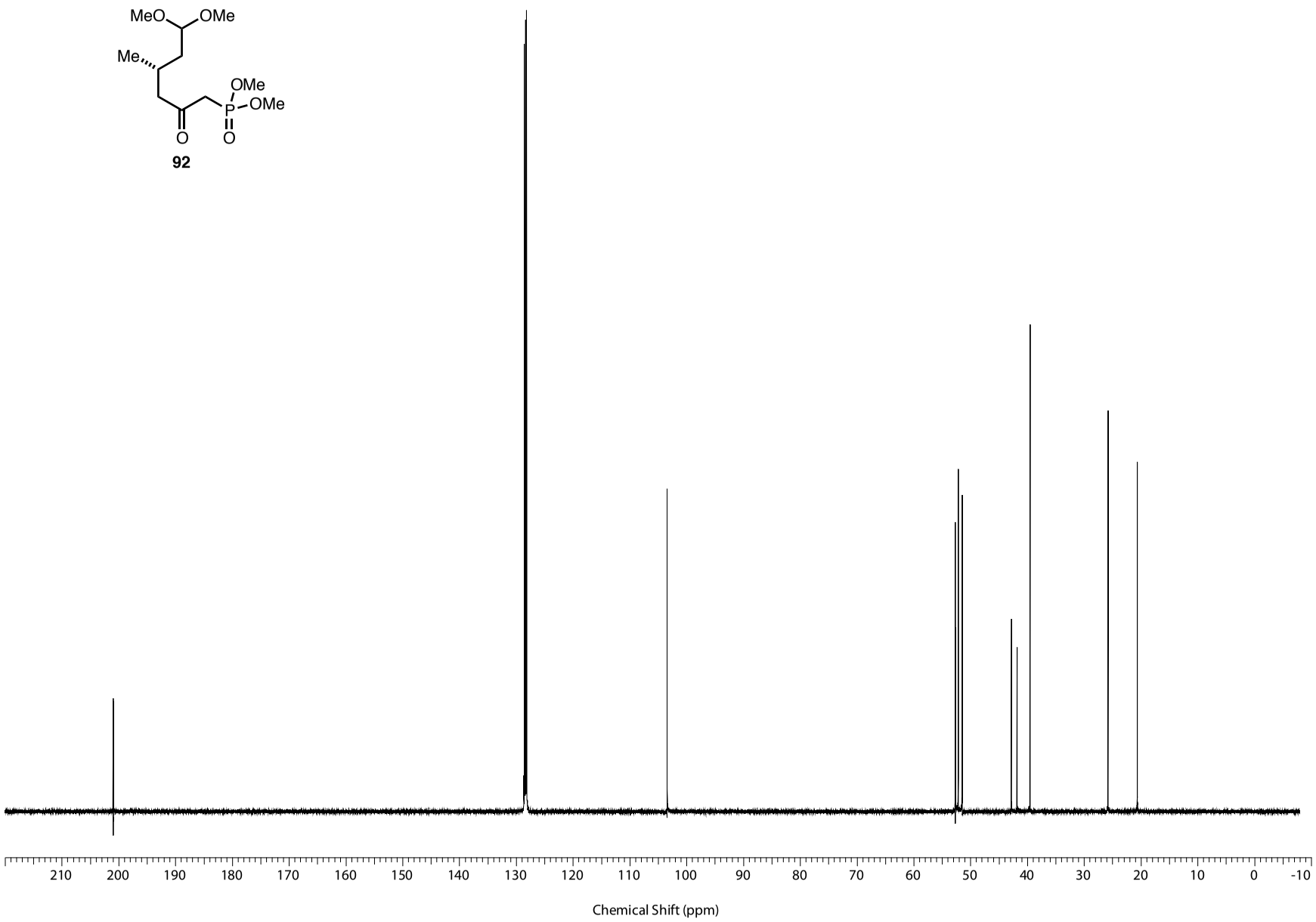
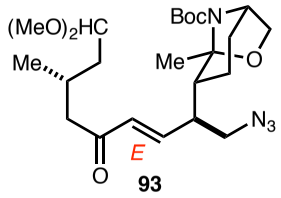
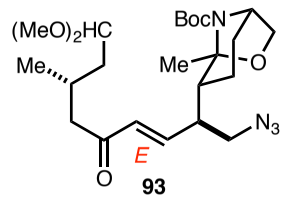
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MeO
OMe
Me
OMe
P
OMe
O
O
92
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


(MeO)2HC
Me
BocN
Me
O
N3
E
O

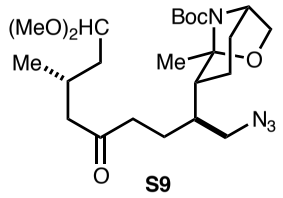
93

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


(MeO)2HC
Me
BocN
Me
O
N3
E
O

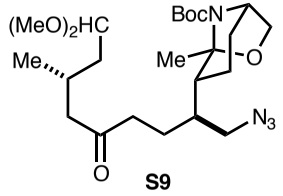
93

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


(MeO)2HC
Me
BocN
Me
O
N3
O

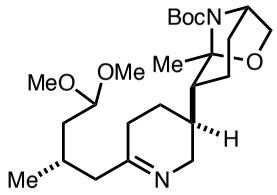
S9

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


(MeO)2HC
Me
BocN
Me
O
N3
O

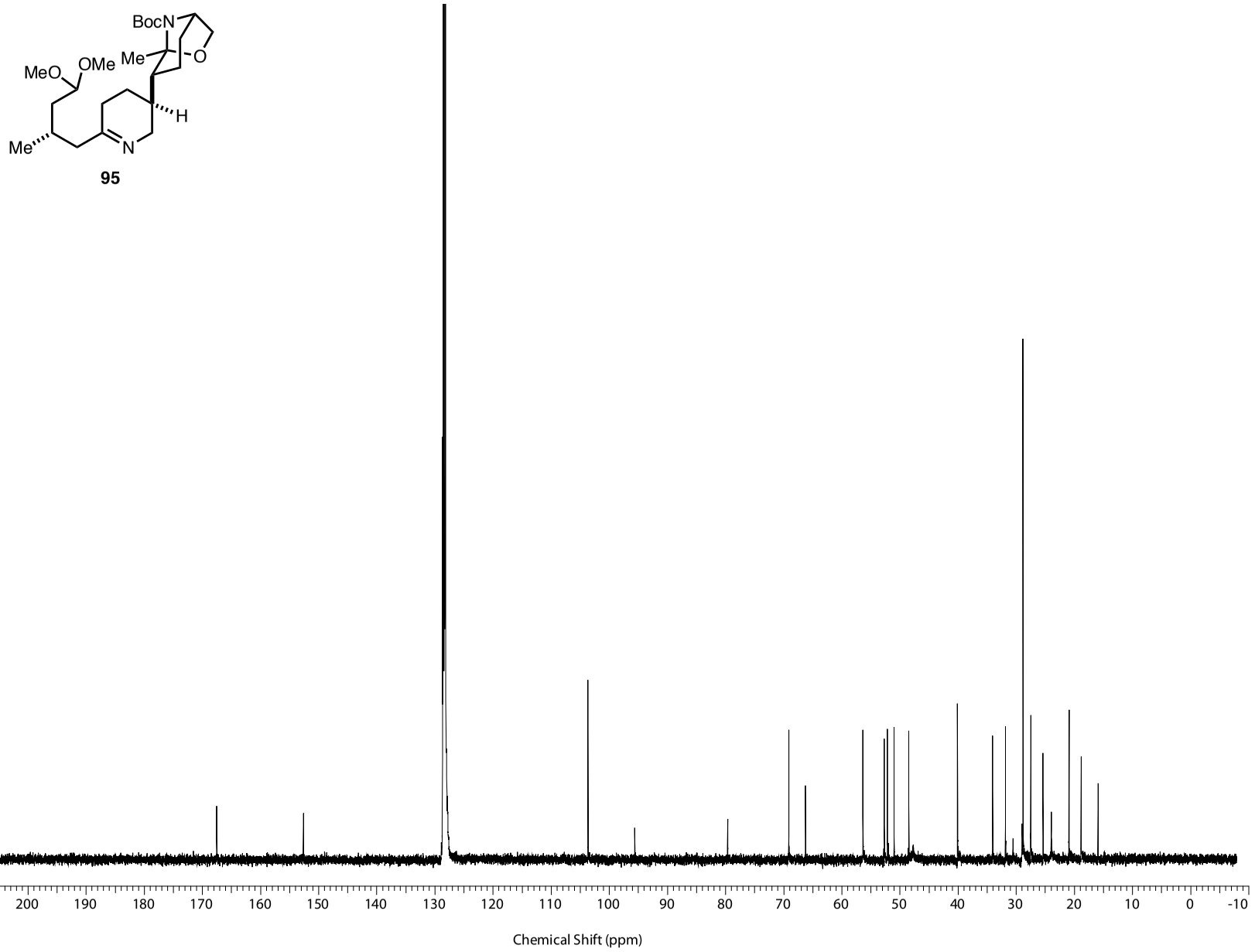
S9

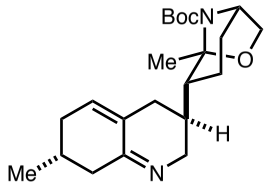
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


BocN
Me
O
MeO
OMe
H
Me
N

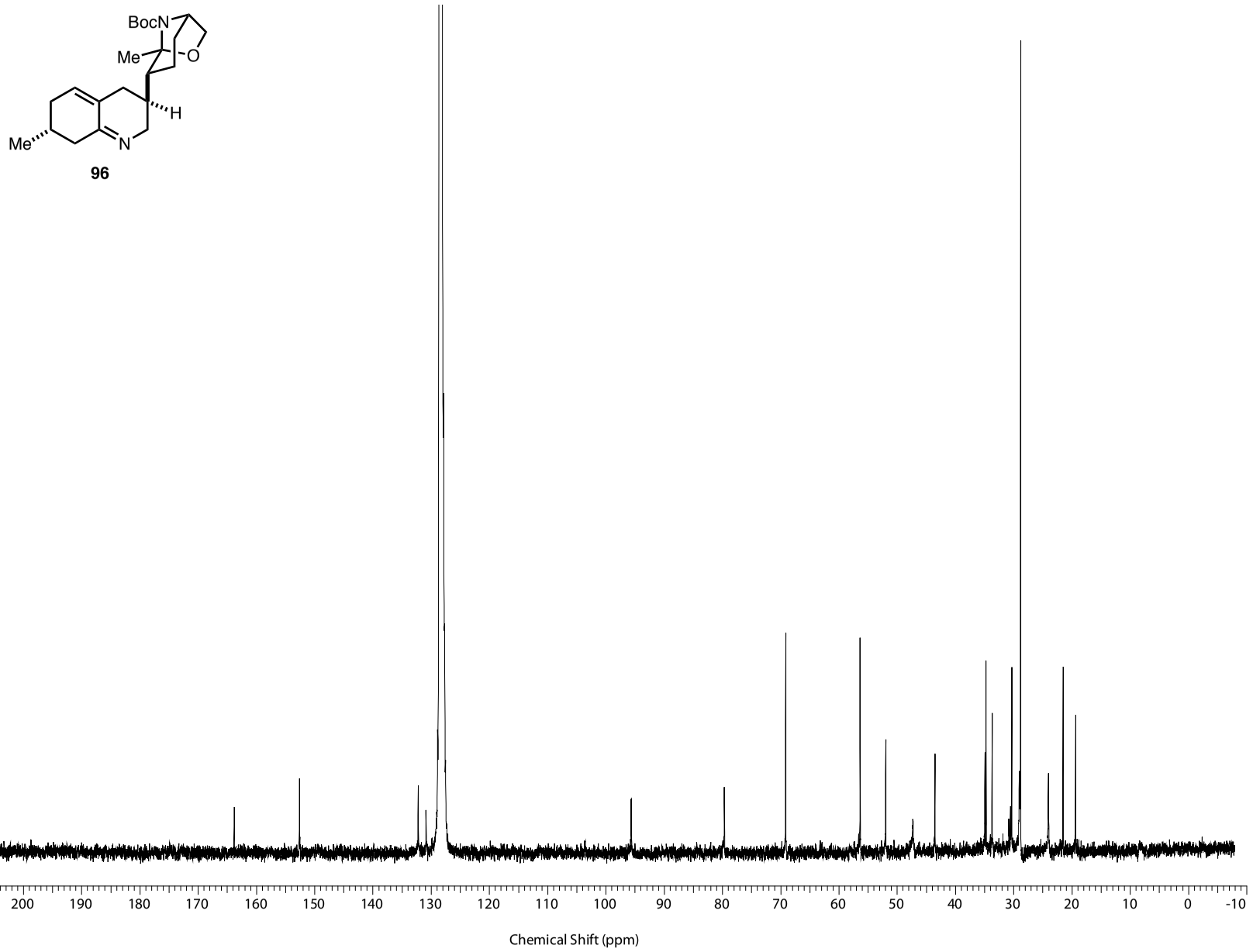
95

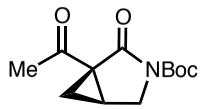
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


BocN
Me
O
MeO
OMe
H
Me
N
95
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

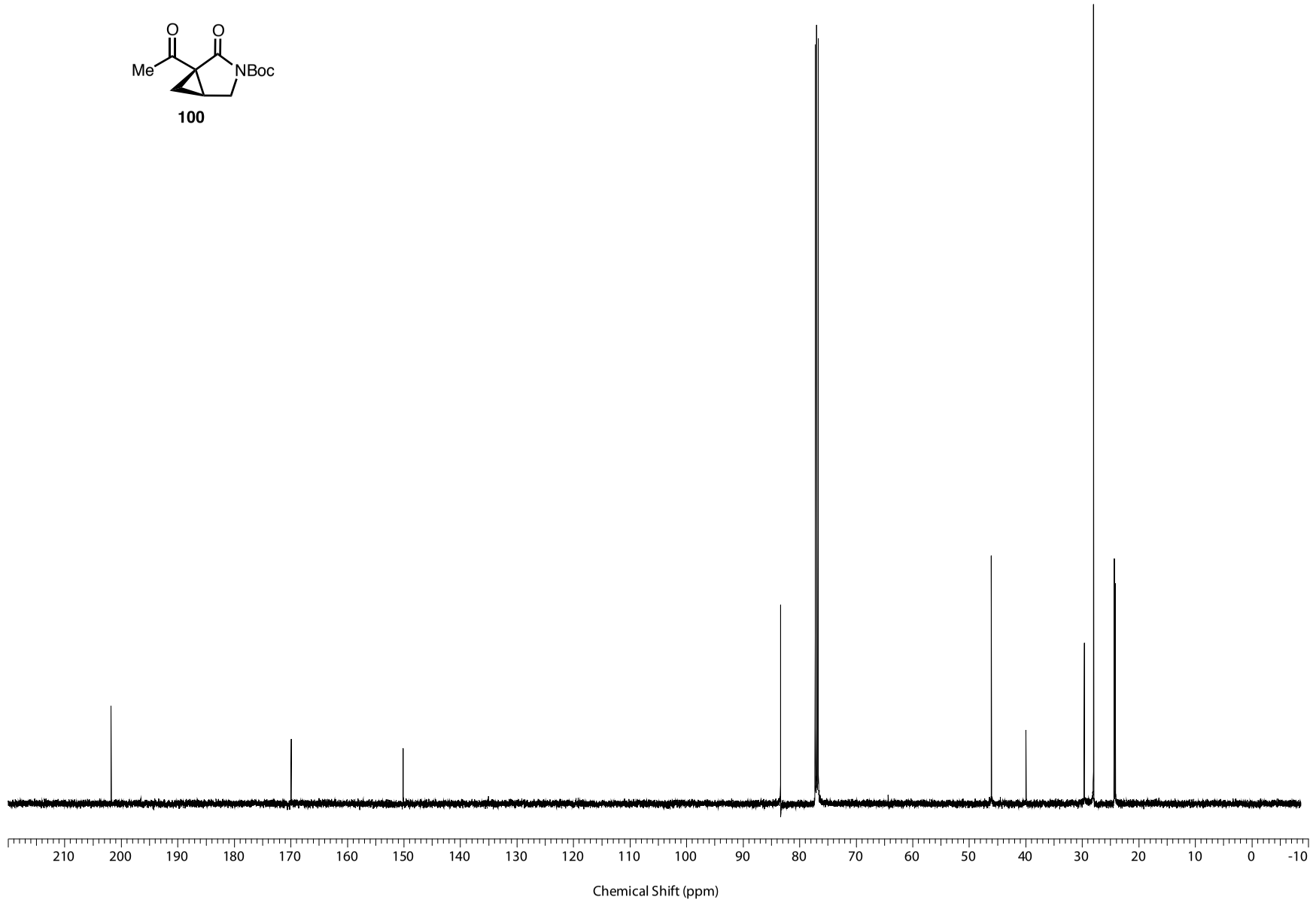


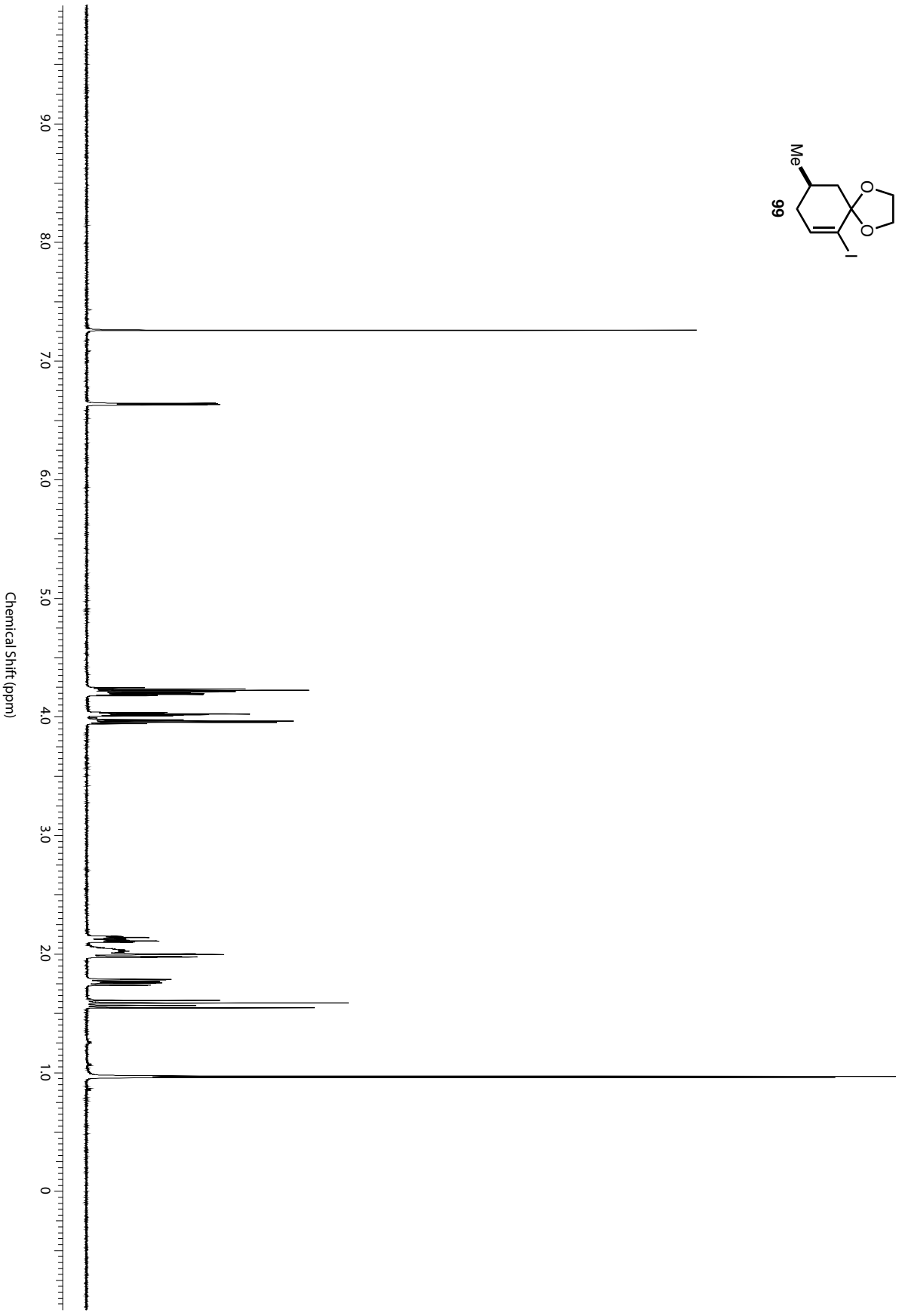
96


BocN
Me
O
H
Me
N
96
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

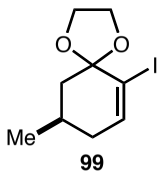


100


O
O
Me
NBoc
100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

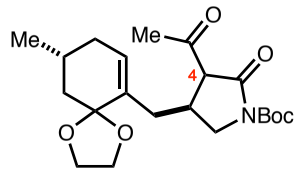


99


O
O
I
Me

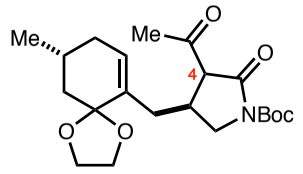
99

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



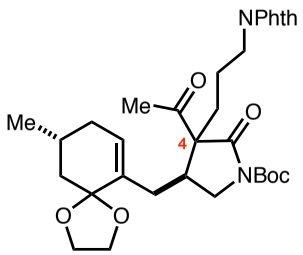
108

>4:1 mixture of C4-diastereomers



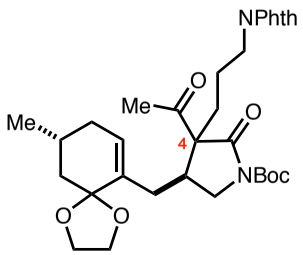
108

>4:1 mixture of C4-diastereomers


NPhth
O
Me
O
Me
4
NBoc
O
O

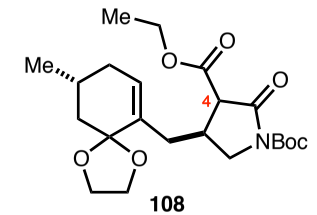
110

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


NPhth
O
Me
O
Me
4
NBoc
O
O

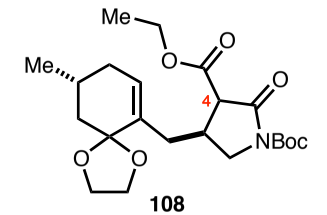
110

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



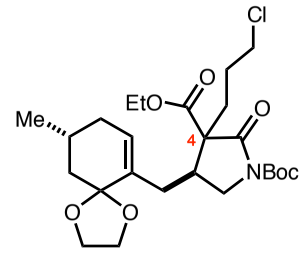
108

>5:1 mixture of C4-diastereomers



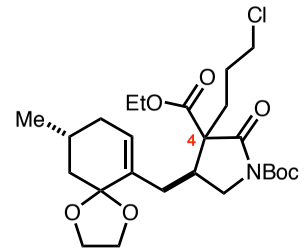
108

>5:1 mixture of C4-diastereomers



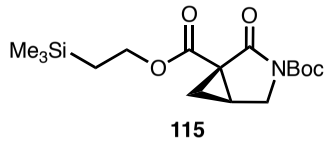
113

>4:1 mixture of C4-diastereomers

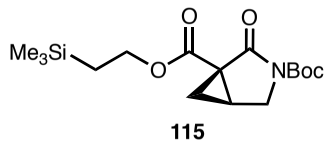


113

>4:1 mixture of C4-diastereomers

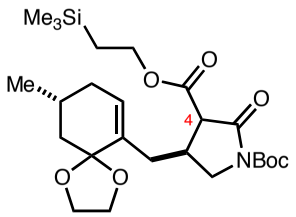


115

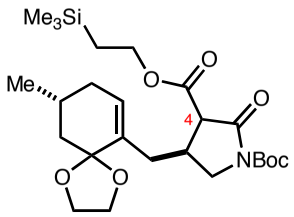

Me3Si
O
O
O
NBoc

115

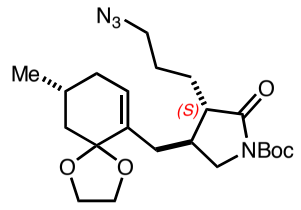
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



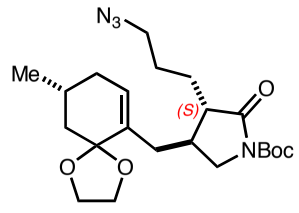
116
>10:1 mixture of C4-epimers



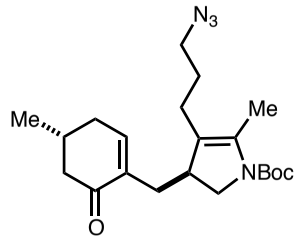
116
>10:1 mixture of C4-epimers



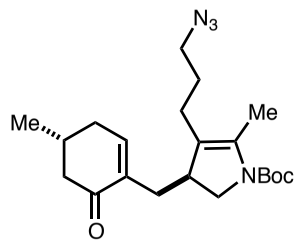
118
>10:1 *trans:cis*



118
>10:1 *trans:cis*

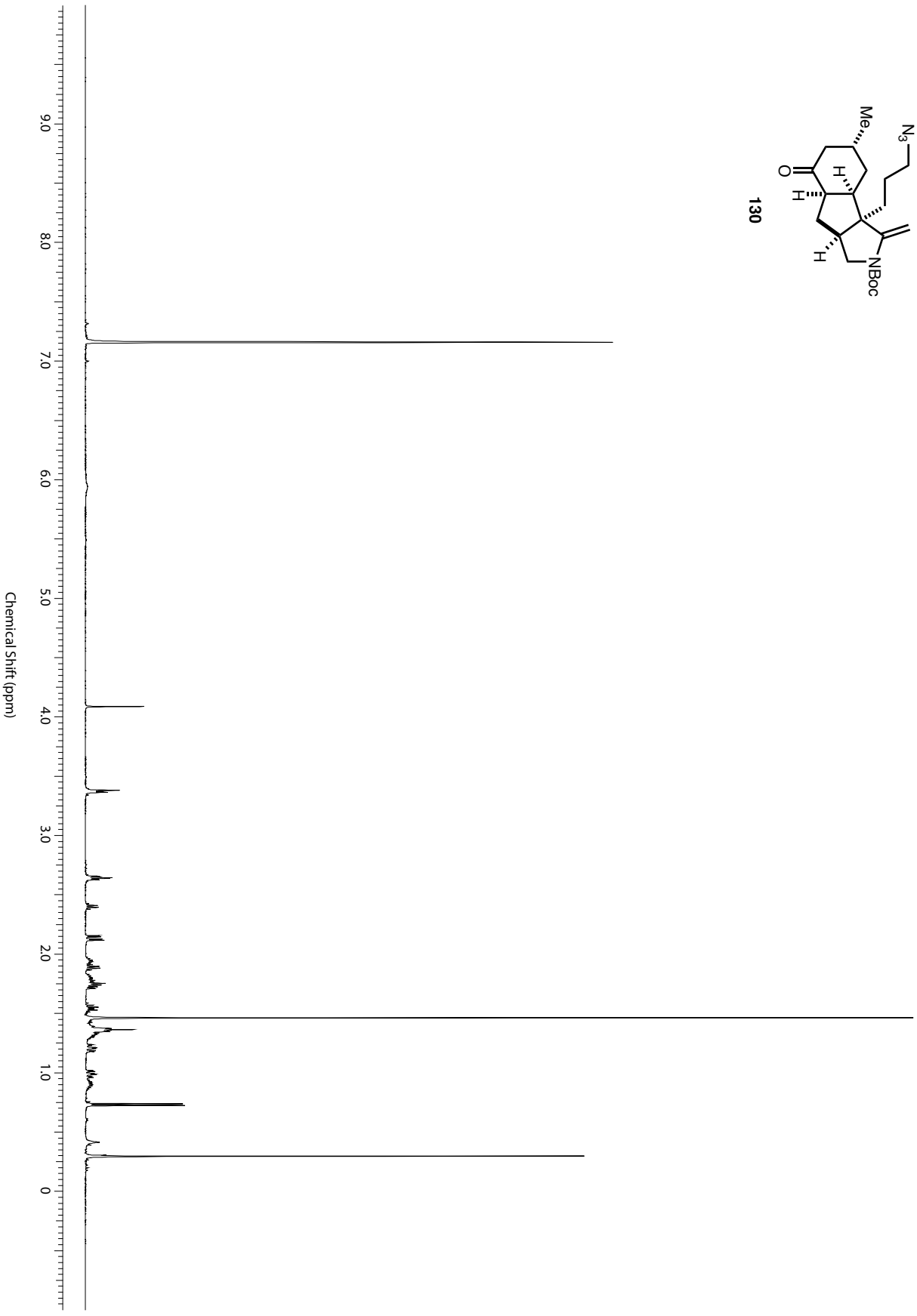


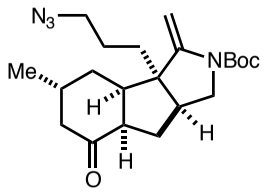
129


N3
Me
Me
NBoc
O

129

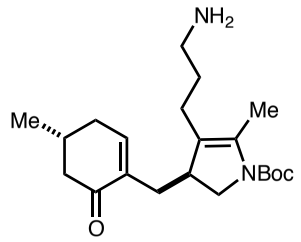
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
N3
H
O
H
H
NBoc
130
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

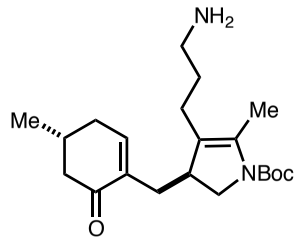

N3
NBoc
Me
H
H
H
O

130

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

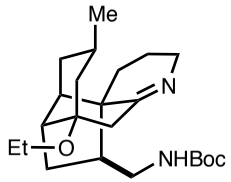


120

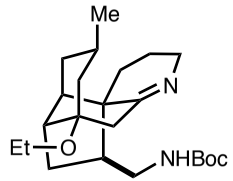

NH2
Me
Me
NBoc
O

120

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

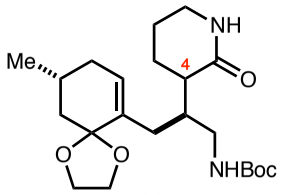


125


Me
N
Et
O
NHBoc

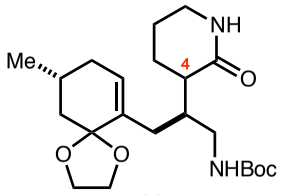
125

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



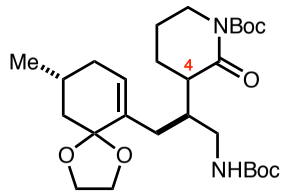
132

~3:2 mixture of C4-epimers



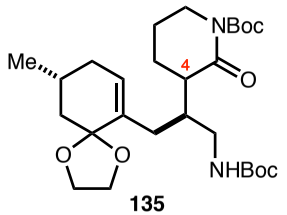
132

~3:2 mixture of C4-epimers



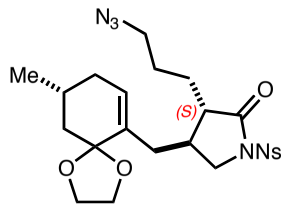
135

~2:1 mixture of C4-epimers

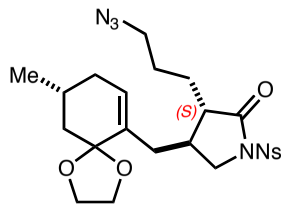


135

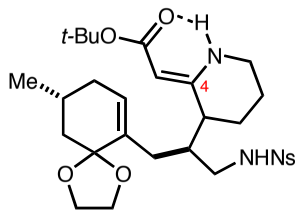
~2:1 mixture of C4-epimers



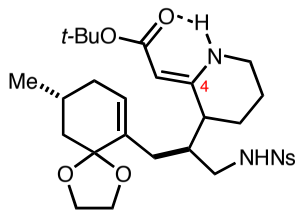
137
>10:1 *trans:cis*



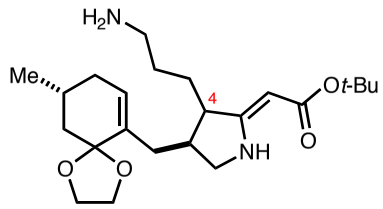
137
>10:1 *trans:cis*



139
~3:2 mixture of C4-epimers

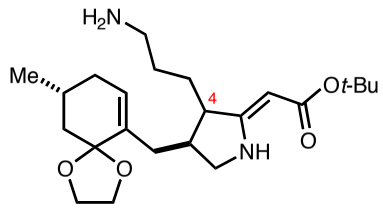


139
~3:2 mixture of C4-epimers



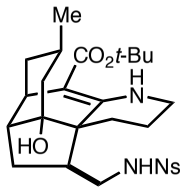
140

~2:1 mixture of C4-epimers



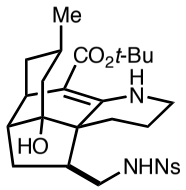
140

~2:1 mixture of C4-epimers


Me
CO2t-Bu
H
N
HO
NHNs

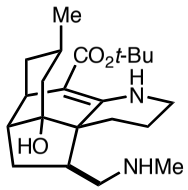
148

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


Me
CO2t-Bu
H
N
HO
NHNs

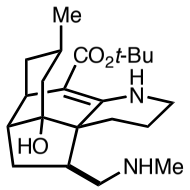
144

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
CO2t-Bu
H
N
HO
NHMe

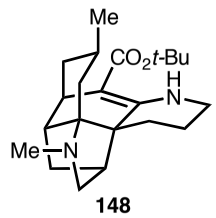
145

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
Chemical Shift (ppm)

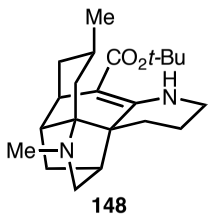

Me
CO2t-Bu
H
N
HO
NHMe

145

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

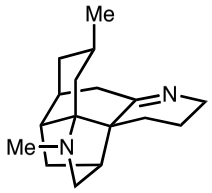


148

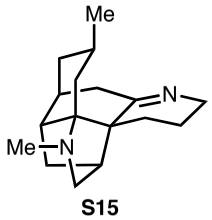

Me
CO2t-Bu
H
N
Me
N

148

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

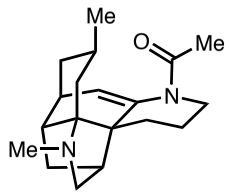


S15

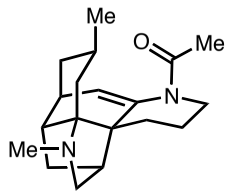

Me
N
Me
N

S15

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



fastigiatine (**37**)

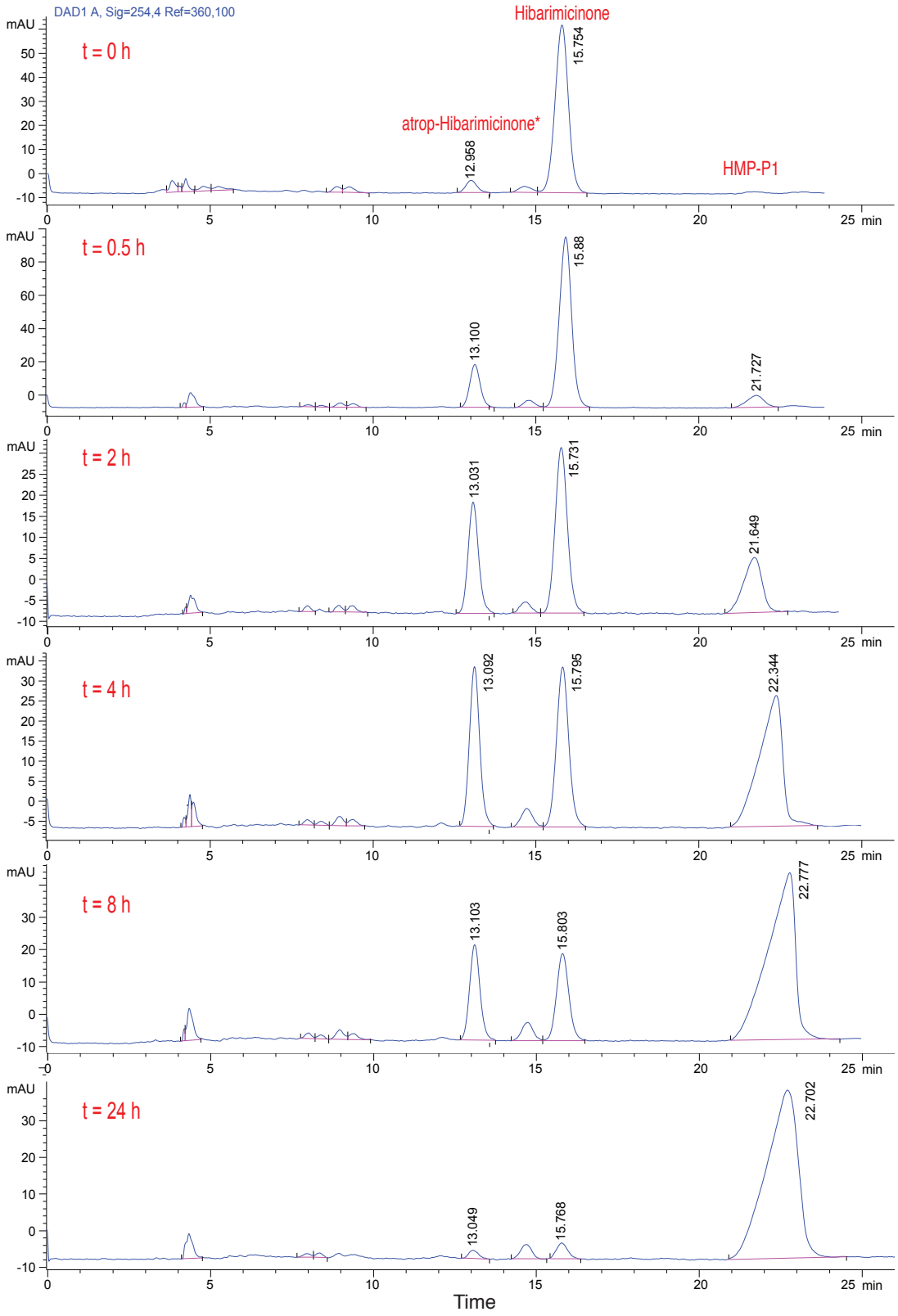


fastigiatine (**37**)

Appendix C

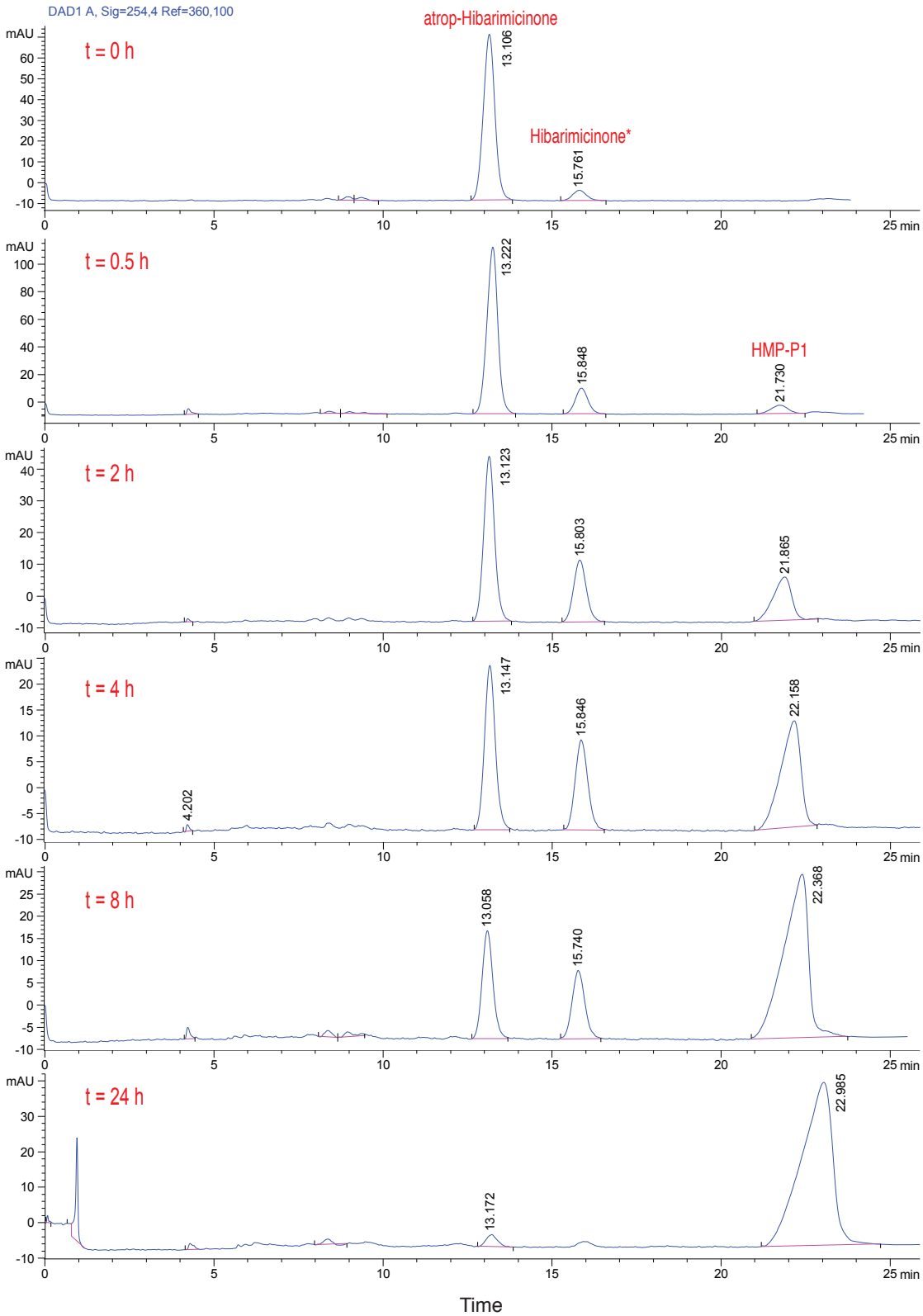
Chapter Four Supplementary Figures

Figure S6. Conversion of Hibarimicinone (**6**) to atrop-Hibarimicinone (**7**) and HMP-P1 (**10**) at RT With pH 7.5 Aqueous Phosphate Buffer in MeOH.



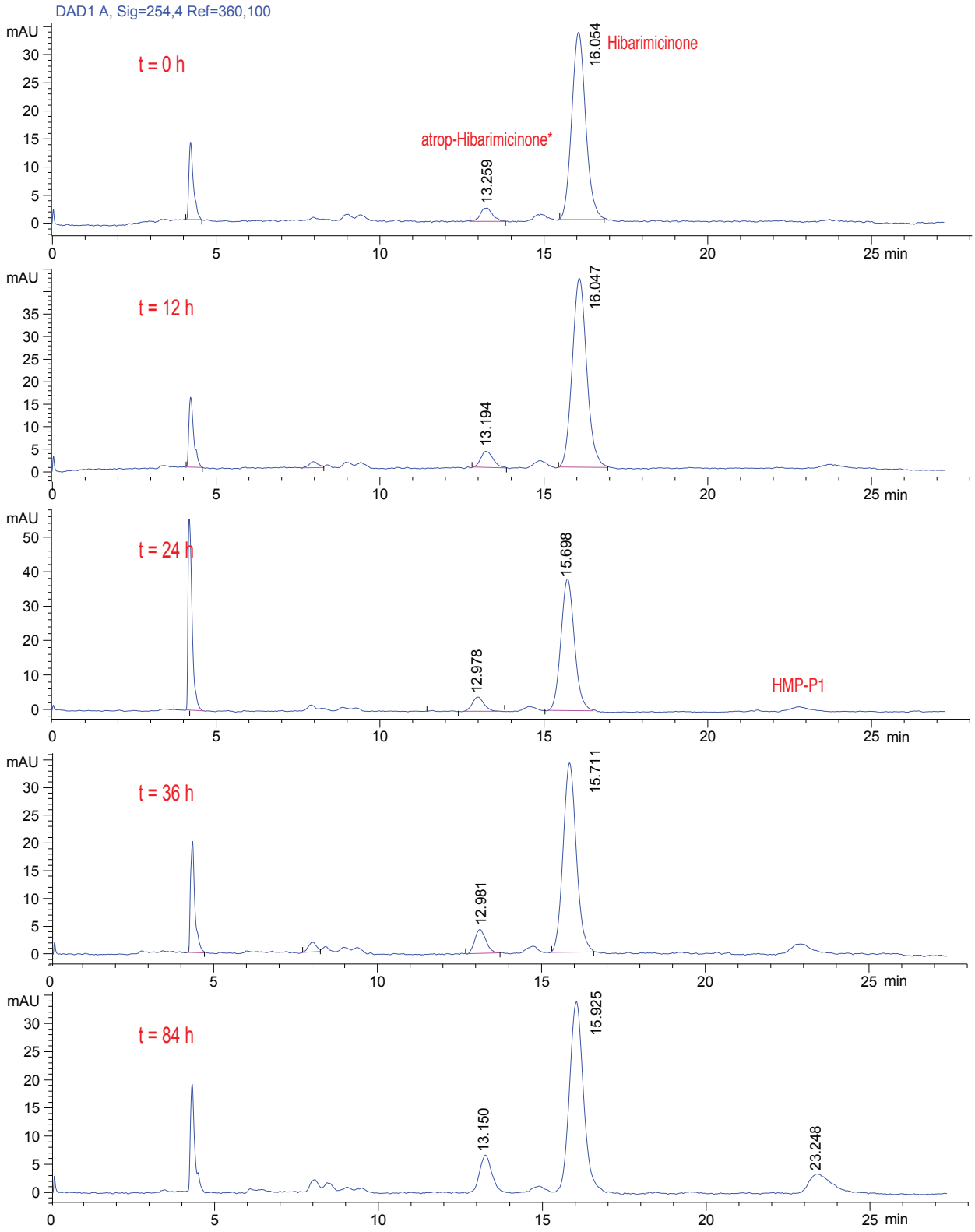
*Minor amounts of atrop-Hibarimicinone form during handling at ambient temperatures.

Figure S7. Conversion of atrop-Hibarimicinone (**7**) to Hibarimicinone (**6**) and HMP-P1 (**10**) at RT With pH 7.5 Aqueous Phosphate Buffer in MeOH.



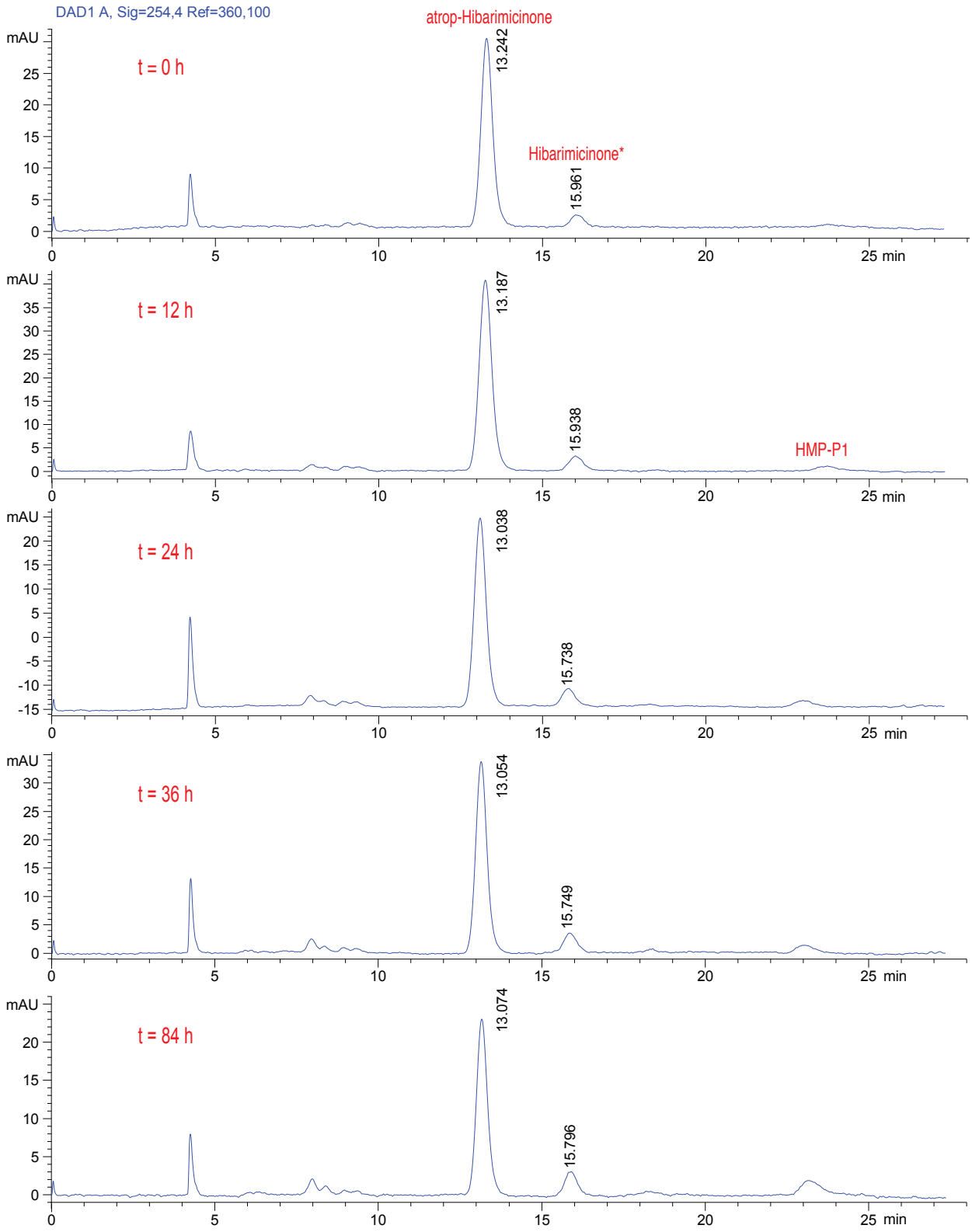
*Minor amounts of Hibarimicinone form during handling at ambient temperatures.

Figure S8. Minor Conversion of Hibarimicinone (**6**) to atrop-Hibarimicinone (**7**) and HMP-P1 (**10**) at RT With HCl in MeOH (1.0 M).



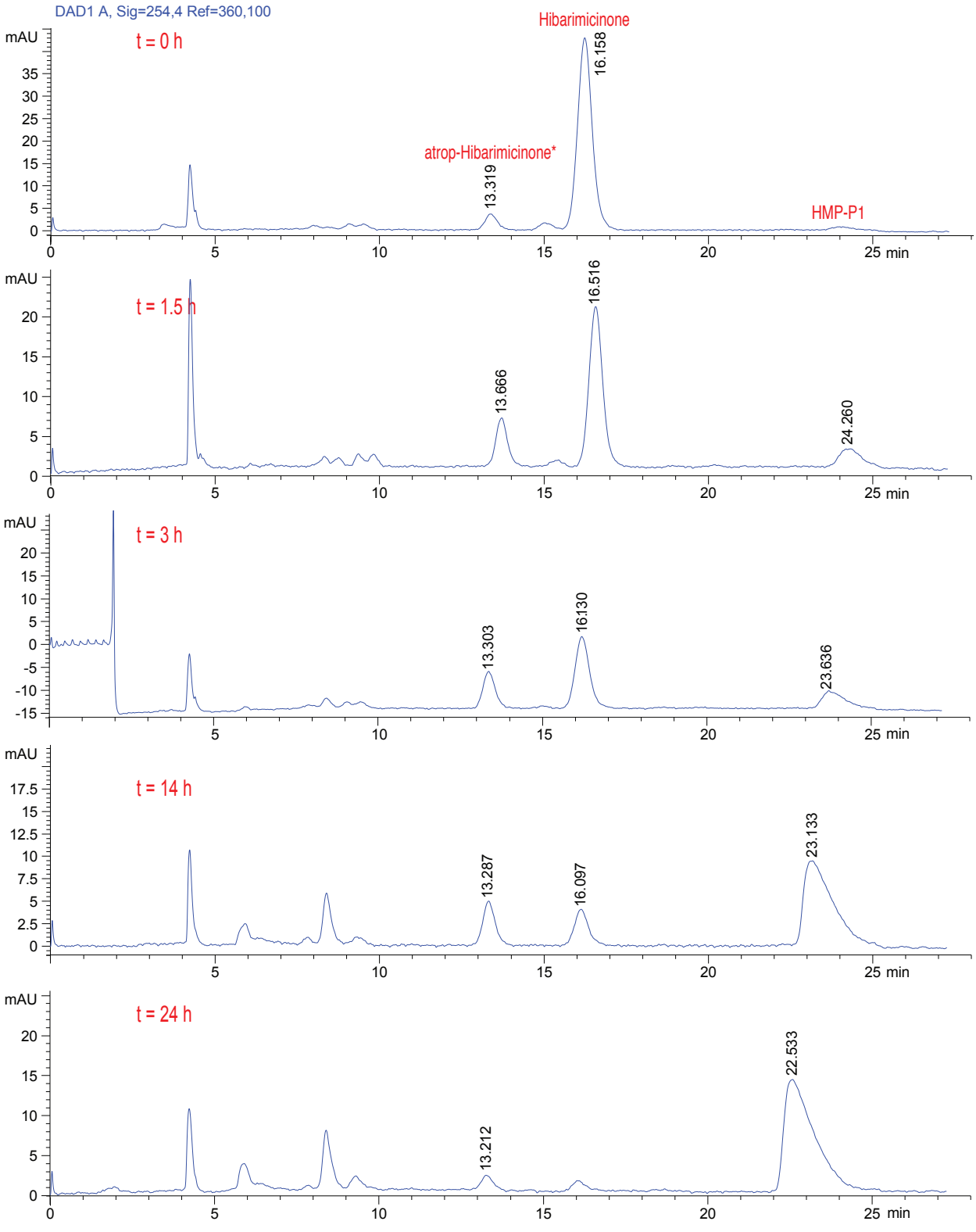
*Minor amounts of atrop-Hibarimicinone form during handling at ambient temperatures.

Figure S9. Minor Conversion of atrop-Hibarimicinone (**7**) to Hibarimicinone (**6**) and HMP-P1 (**10**) at RT With HCl in MeOH (1.0 M).



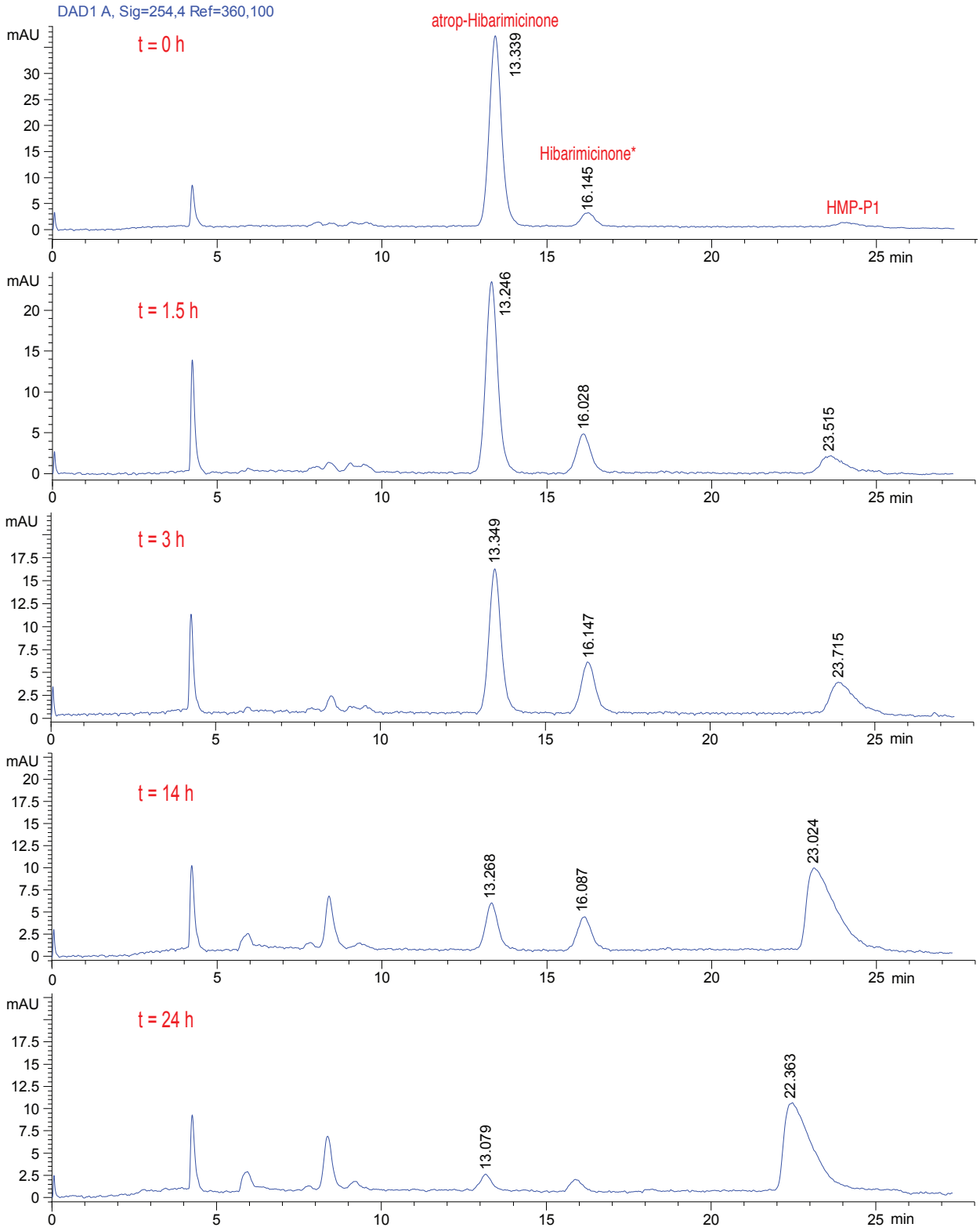
*Minor amounts of Hibarimicinone form during handling at ambient temperatures.

Figure S10. Conversion of Hibarimicinone (**6**) to Hibarimicinone (**7**) and HMP-P1 (**10**) at 60 °C With HCl in MeOH (1.0 M).



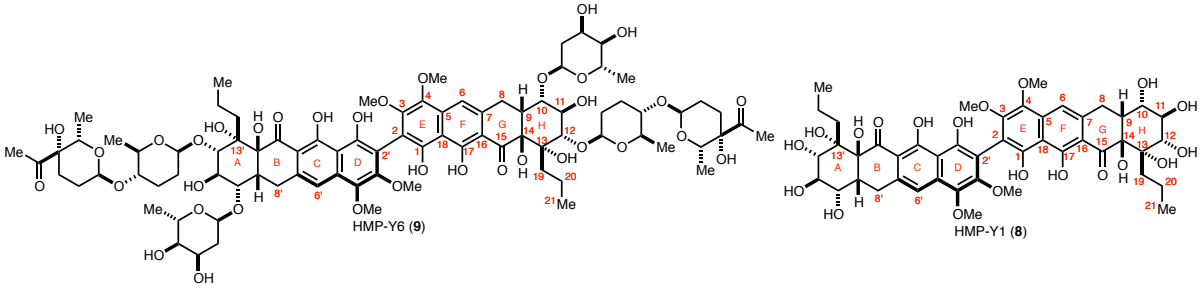
*Minor amounts of atrop-Hibarimicinone form during handling at ambient temperatures.

Figure S11. Conversion of atrop-Hibarimicinone (**7**) to Hibarimicinone (**6**) and HMP-P1 (**10**) at 60 °C With HCl in MeOH (1.0 M).



*Minor amounts of Hibarimicinone form during handling at ambient temperatures.

Table S4. ^{13}C NMR data comparison between synthetic HMP-Y1 (**8**) and natural HMP-Y6 (**9**) aglycon carbon resonances.[148]



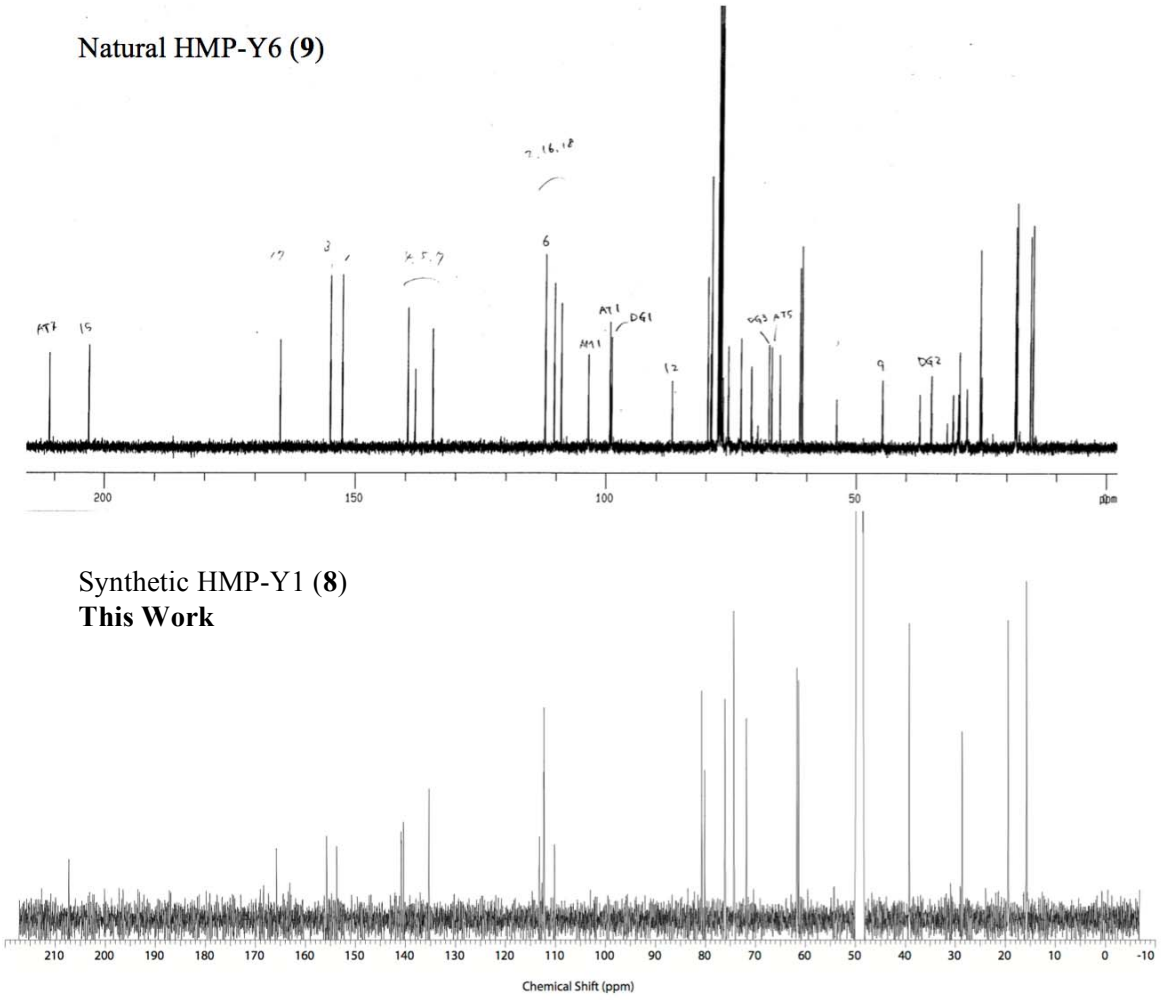
HMP-Y6 (9), Igarashi et. al.[149] (^{13}C, 100 MHz, $CDCl_3$)	**This Work, HMP-Y1 (8)** (^{13}C, 126 MHz, CD_3OD)[150]
203.2 (C15)	207.3
165.0 (C17)	165.8
155.1 (C3)	155.7
152.6 (C1)	153.7
139.5 (C7)	140.9
138.1 (C4)	140.5
134.6 (C5)	135.3
112.21 (C6)	113.3
112.21 (C2)	112.4
110.4 (C16)	112.3
109.0 (C18)	110.2
86.9 (C12)	80.8
79.7 (C13)	80.2
77.4 (C10)	76.1
76.7 (C10)	74.3
71.0 (C11)	71.8
61.5 (4-OMe)	61.7
61.0 (3-OMe)	61.3
44.9 (C9)	48.4
37.4 (C19)	39.2
28.0 (C8)	28.6
18.3 (C20)	19.4
15.4 (C21)	15.7

[148] No ^{13}C NMR data for HMP-Y1 (**8**) was previously recorded according to a private communication with Prof. Y. Igarashi.

[149] Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 61–70. The reference points for the residual protium and carbon resonances of the NMR solvent were not listed.

[150] The ^{13}C NMR of **8** was taken in CD_3OD due to low solubility in $CDCl_3$.

Figure S12. ^{13}C NMR data comparison between synthetic HMP-Y1 (**8**) in CD_3OD and natural HMP-Y6 (**9**) in $CDCl_3$.[148,150,151]

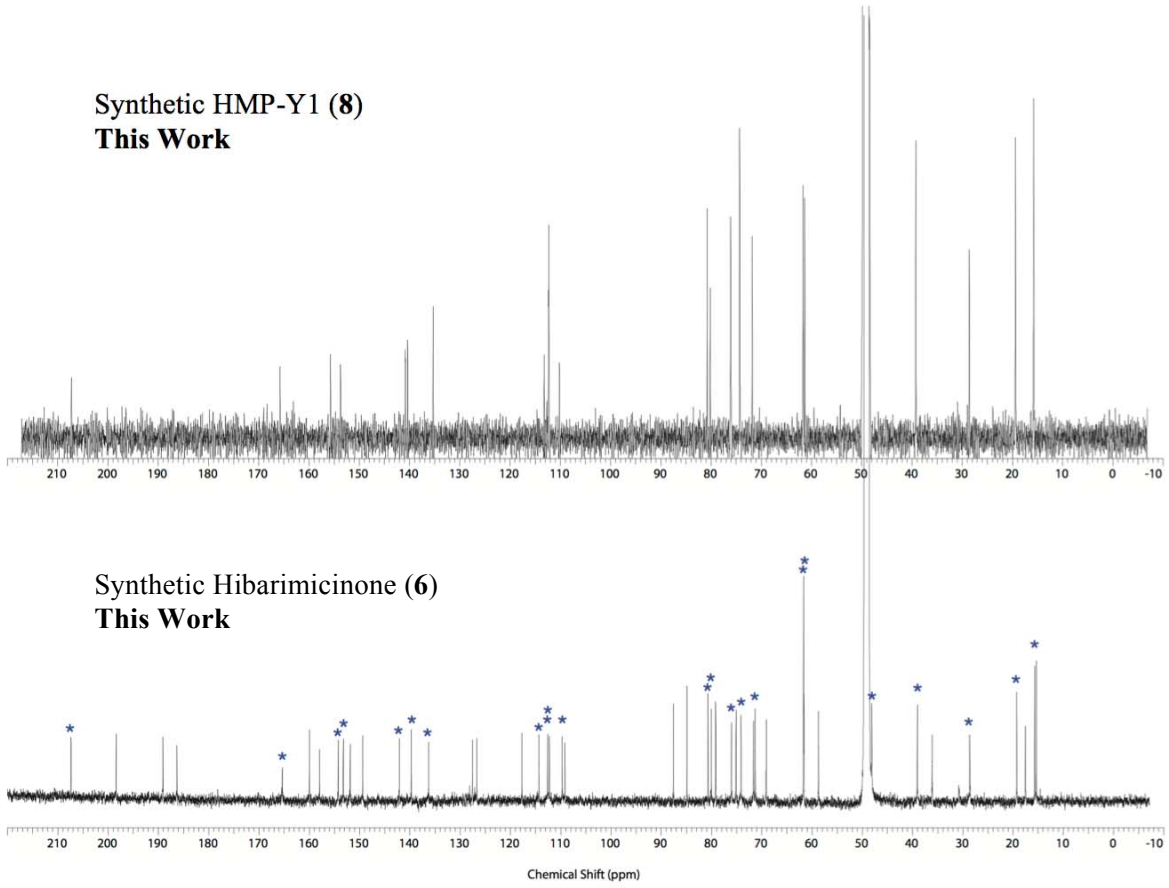


[151] ^{13}C NMR spectrum of HMP-Y6 (**9**) was obtained through a private communication with Y. Igarashi.

Table S5. ^{13}C NMR data comparison between synthetic HMP-Y1 (**8**) and hibarimicinone (**6**).

Hibarimicinone (**6**) (^{13}C, 126 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1)	**HMP-Y1** (**8**) (^{13}C, 126 MHz, CD_3OD)
207.4	207.3
198.4	
189.1	
186.3	
165.4	165.8
160.0	
158.0	
154.2	155.7
153.3	153.7
151.9	
149.4	
142.1	140.9
139.7	140.5
136.3	135.3
127.5	
126.7	
117.7	
114.3	113.3
112.6	112.4
112.3	112.3
109.7	110.2
109.2	
87.6	
84.9	
80.7	80.8
80.1	80.2
79.2	
76.0	76.1
75.1	
74.1	74.3
71.6	71.8
71.3	
69.1	
61.7	
61.7	61.7
61.6	61.3
58.7	
48.1	48.4
39.0	39.2
36.1	
28.6	28.6
19.3	19.4
17.6	
15.7	
15.3	15.7

Figure S13. Comparison of ^{13}C NMR (126 MHz) spectra of synthetic hibarimicinone (**6**) and HMP-Y1 (**8**).



*Denotes carbon resonances of **6** that are similar to that of **8**.

Table S6. ^{1}H NMR data comparison between synthetic HMP-Y1 (**8**) and hibarimicinone (**6**).

Hibarimicinone (**6**) (^{1}H, 600 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1)	**HMP-Y1** (**8**) (^{1}H, 600 MHz, CD_3OD)
7.35 (s, 1H)	7.34 (s, 2H)
5.83 (s, 1H)	
4.10–4.05 (m, 2H)	4.08 (dd, *J* = 5.5, 9.6 Hz, 2H)
3.98 (d, *J* = 7.9 Hz, 1H)	
3.97 (s, 3H)	
3.96–3.92 (m, 1H)	3.94 (t, *J* = 9.4 Hz, 2H)
3.94 (s, 3H)	3.88 (s, 6H)
3.85 (s, 3H)	3.84 (s, 6H)
3.80 (t, *J* = 8.5 Hz, 1H)	
3.73 (d, *J* = 9.4 Hz, 1H) 3.75–3.69 (m, 1H)	3.78–3.68 (m, 4H),
3.18 (dd, *J* = 6.0, 17.1 Hz, 1H)	3.18 (dd, *J* = 4.6, 16.5 Hz, 2H)
2.65 (td, *J* = 5.6, 13.3 Hz, 1H)	2.66 (dt, *J* = 5.3, 13.3 Hz, 2H)
2.57 (d, *J* = 3.8 Hz, 1H)	
1.88 (dt, *J* = 4.2, 13.4 Hz, 1H)	1.88–1.79 (m, 2H)
1.81 (dt, *J* = 4.2, 13.4 Hz, 1H) 1.77–1.65 (m, 2H)	1.79–1.65 (m, 4H)
1.51–1.41 (m, 1H)	
1.39–1.30 (m, 1H)	1.44–1.32 (m, 2H)
1.26–1.18 (m, 1H)	
1.01 (dt, *J* = 4.2, 13.4 Hz, 1H)	
0.88 (t, *J* = 7.0 Hz, 2H)	0.89 (t, *J* = 6.6 Hz, 6H)
0.79 (t, *J* = 7.2 Hz, 2H)	

Figure S14. ^{1}H NMR data (600 Mhz) comparison between synthetic HMP-Y1 (**8**) and hibarimicinone (**6**).

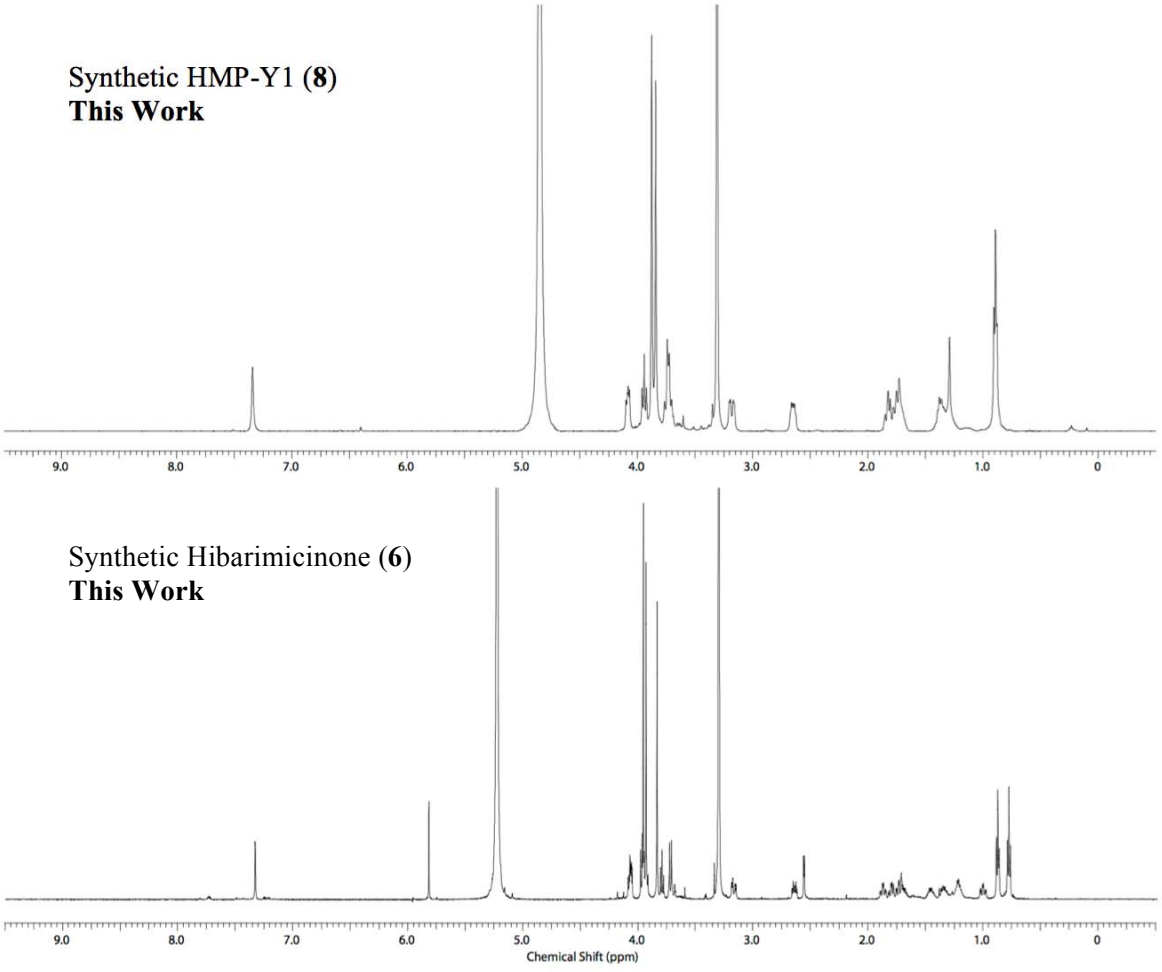
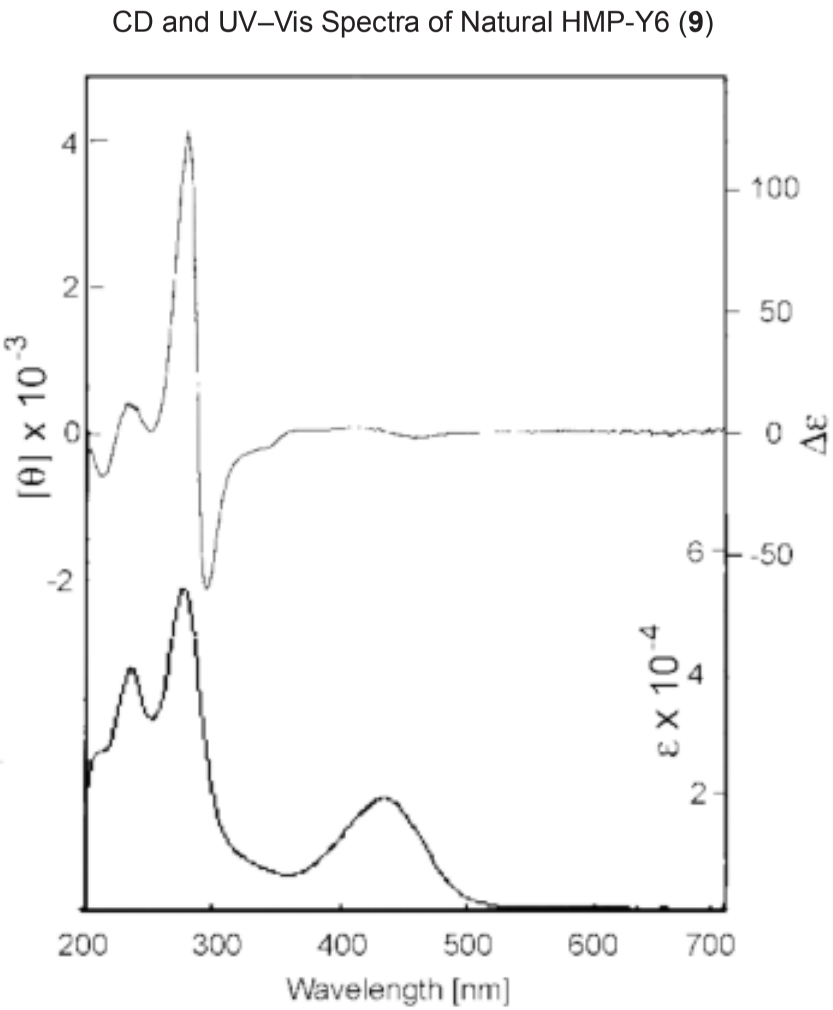


Figure S15. Comparison of UV–Vis Spectra of Natural HMP-Y6 (**9**) and with Synthetic HMP-Y1 (**8**) and atrop-HMP-Y1 (**110**).



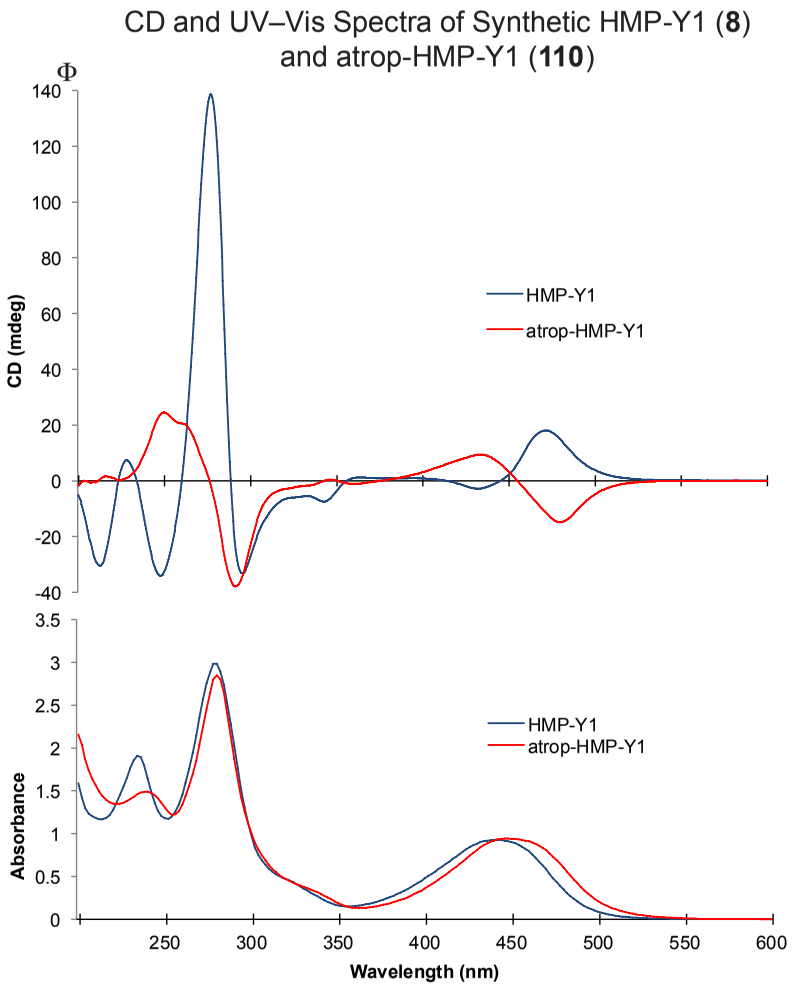


Table S7. ^{1}H NMR data comparison between reported synthetic hibarimicinone (**6**) and our synthetic hibarimicinone (**6**).

Tatsuta et. al. Report[152,153] (^{1}H, 400 MHz, CD_3OD, pH 1)	**This Work** (^{1}H, 400 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1)
7.35 (s, 1H)	7.35 (s, 1H)
5.84 (s, 1H)	5.84 (s, 1H)
4.09 (dd, *J* = 5.5 Hz, 10.0 Hz, 1H) 4.08 (dd, *J* = 3.5, 8.0 Hz, 1H)	4.12–4.04 (m, 2H)
3.99 (d, *J* = 8.0 Hz, 1H) 3.99–3.93 (m, 1H)	4.01–3.92 (m, 2H)
3.97 (s, 3H)	3.97 (s, 3H)
3.95 (s, 3H)	3.95 (s, 3H)
3.85 (s, 3H)	3.85 (s, 3H)
3.81 (t, *J* = 8.0, 8.0 Hz, 1H)	3.80 (t, *J* = 8.2 Hz, 1H)
3.74 (d, *J* = 9.0 Hz, 1H)	3.73 (d, *J* = 9.1 Hz, 1H)
3.73 (dd, *J* = 13.5, 17.0 Hz, 1H)	3.78–3.68 (m, 1H)
3.19 (dd, *J* = 5.5, 17.0 Hz, 1H)	3.18 (dd, *J* = 5.8, 17.2 Hz, 1H)
2.66 (td, *J* = 5.5, 13.5, Hz, 1H)	2.65 (td, *J* = 5.7, 13.4 Hz, 1H)
2.59 (d, *J* = 3.5 Hz, 1H)	2.57 (d, *J* = 3.7 Hz, 1H)
1.89 (dt, *J* = 4.0, 13.0 Hz, 1H)	1.88 (dt, *J* = 3.8, 13.0 Hz, 1H)
1.81 (dt, *J* = 4.0, 11.0 Hz, 1H) 1.75 (dt, *J* = 3.5, 11.0 Hz, 1H) 1.78–1.64 (m, 1H)	1.83–1.63 (m, 3H)
1.53–1.40 (m, 1H)	1.53–1.41 (m, 1H)
1.40–1.16 (m, 2H)	1.40–1.29 (m, 1H) 1.28–1.15 (m, 1H)
1.01 (dt, *J* = 4.0, 13.0 Hz, 1H)	1.01 (dt, *J* = 3.9, 13.0 Hz, 1H)
0.89 (t, *J* = 7.0 Hz, 3H)	0.89 (t, *J* = 7.0 Hz, 3H)
0.79 (t, *J* = 7.0 Hz, 3H)	0.79 (t, *J* = 7.2 Hz, 3H)

[152] Tatsuta, K.; Fukuda, T.; Ishimori, T.; Yachi, R.; Yoshida, S.; Hashimoto, H.; Hosokawa, S. *Tetrahedron Lett.* **2012**, *53*, 422–425.

[153] The reference points for the residual protium and carbon resonances of the NMR solvent were not listed.

Figure S16. Comparison of ^{1}H NMR spectra (400 MHz) of natural and synthetic hibarimicinone (**6**).

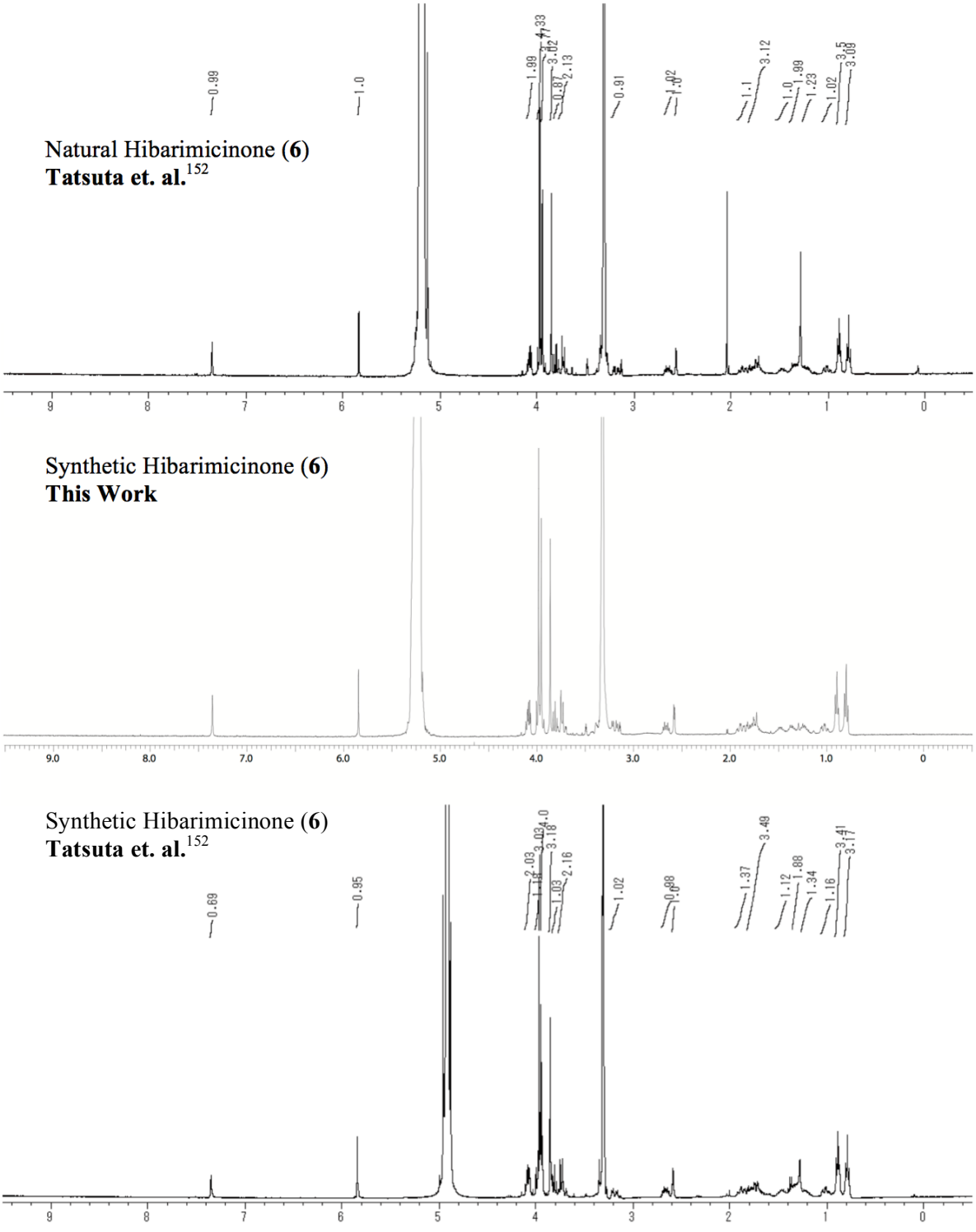


Table S8. ^{13}C NMR data comparison between reported synthetic hibarimicinone (**6**) and our synthetic hibarimicinone (**6**).

Tatsuta et. al. Report[152,153] (^{13}C, 150 MHz, CD_3OD, pH 1)	**This Work** (^{13}C, 126 MHz, ~50:1 CD_3OD/20 wt.% DCl in D_2O, pD ~1)
207.3	207.4
198.5	198.4
189.0	189.1
186.2	186.3
165.2	165.4
159.9	160.0
157.8	158.0
154.1	154.2
153.1	153.3
151.8	151.9
149.2	149.4
142.0	142.1
139.6	139.7
136.2	136.3
127.4	127.5
126.5	126.7
117.6	117.7
114.3	114.3
112.5	112.6
112.1	112.3
109.6	109.7
109.1	109.2
87.5	87.6
84.8	84.9
80.6	80.7
80.0	80.1
79.0	79.2
75.8	76.0
75.0	75.1
74.0	74.1
71.5	71.6
71.2	71.3
69.0	69.1
61.5	61.7
61.5	61.7
61.5	61.6
58.6	58.7
48.0	48.1
38.9	39.0
35.9	36.1
28.5	28.6
19.1	19.3

Table S8. (continued)	
17.4	17.6
15.5	15.7
15.2	15.3

Figure S17. Comparison of ^{13}C NMR spectra of synthetic hibarimicinone (**6**).

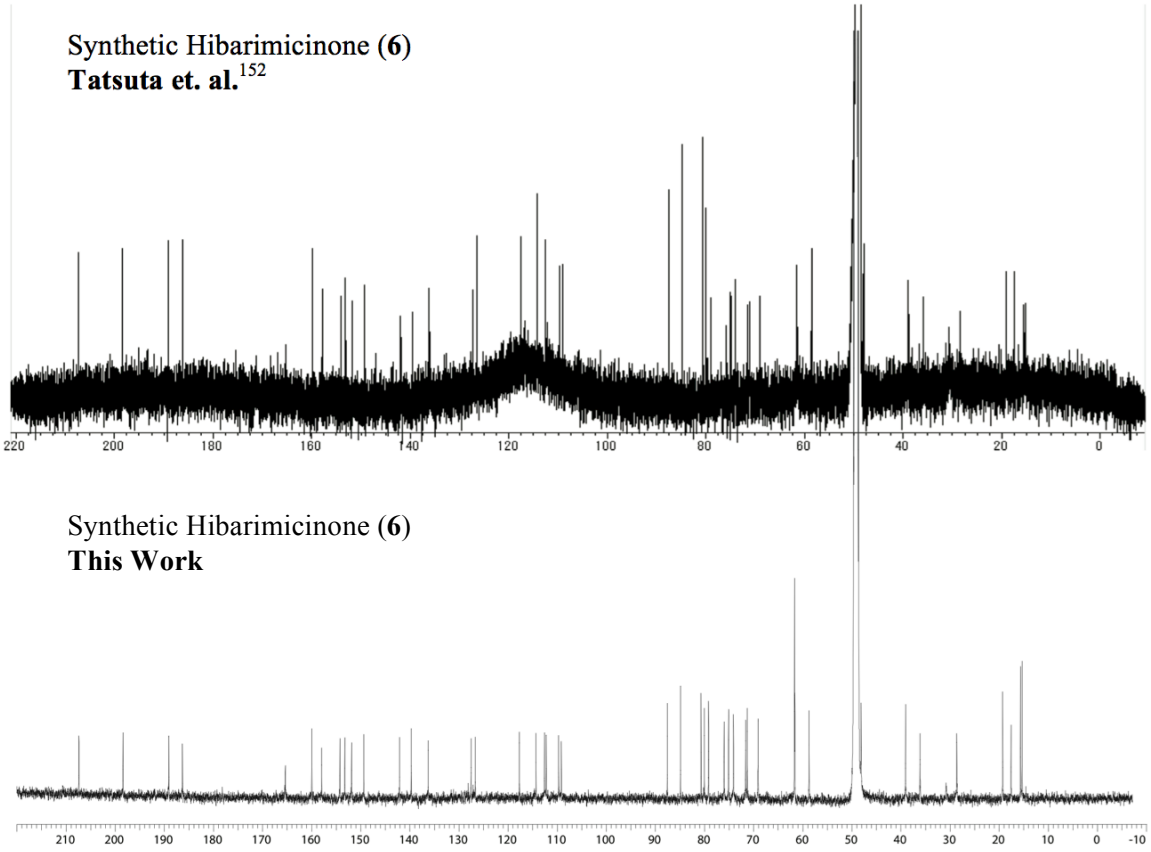
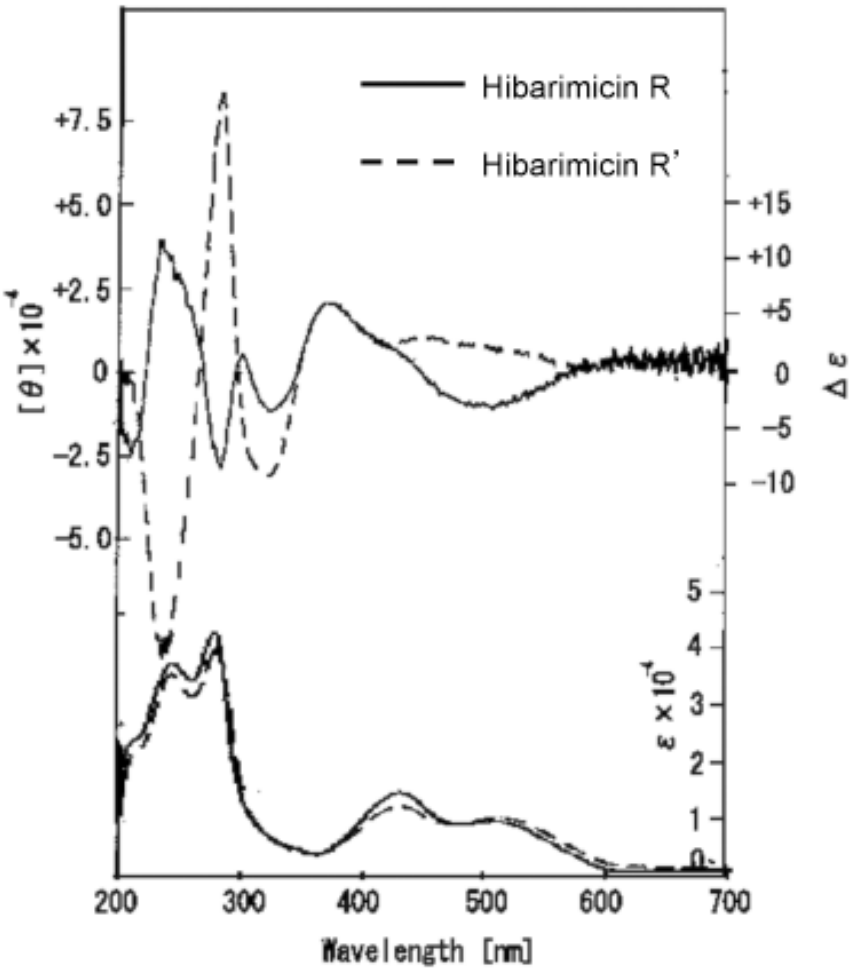


Figure S18. Comparison of UV–Vis Spectra of Natural Hibarimicione (**6**) and atrop-Hibarimicinone (**7**) with Our Synthetic **6** and **7**.

CD and UV–Vis Spectra of Natural Hibarimicinone (**6**, Hibarimicin R) and atrop-Hibarimicinone (**7**, Hibarimicin R')



CD and UV–Vis Spectra of Synthetic Hibarimicinone (**6**) and atrop-Hibarimicinone (**7**)

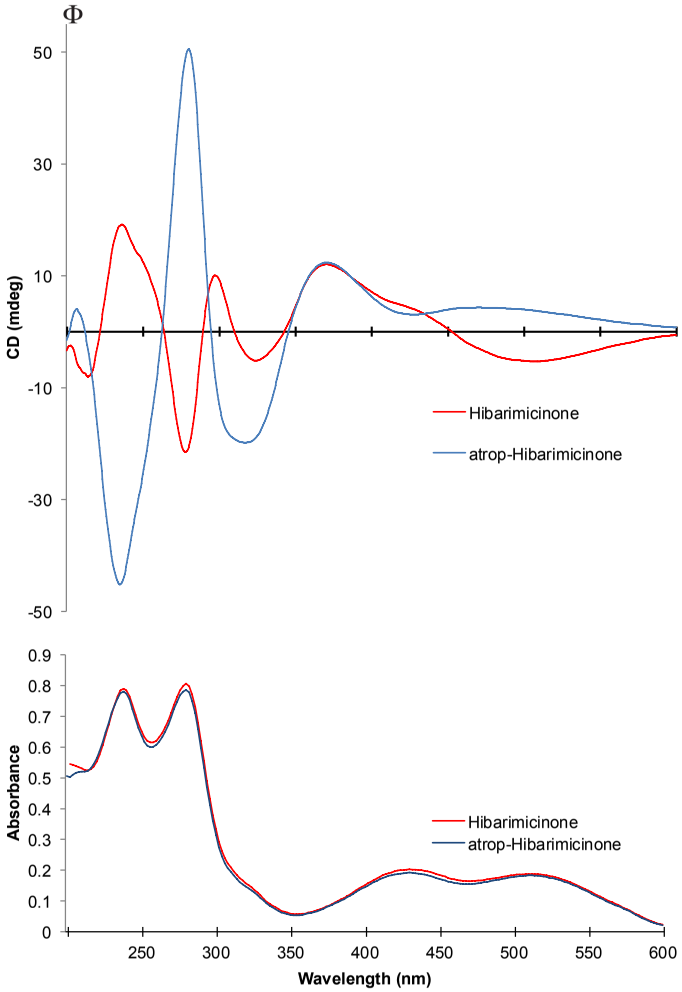
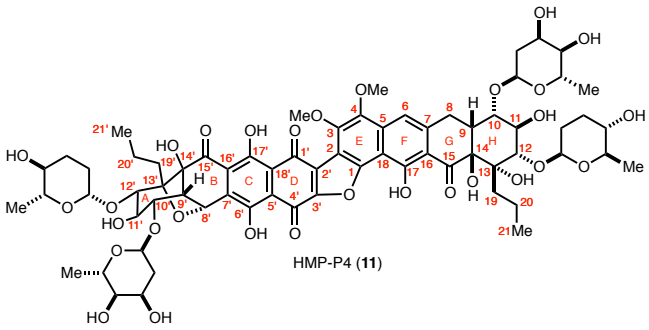
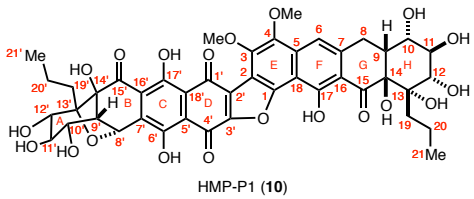


Table S9. ^{13}C NMR data comparison between synthetic HMP-P1 (**10**) and natural HMP-P4 (**11**) aglycon carbon resonances.[154]





HMP-P4 (11), Igarashi et. al.[155,156] (^{13}C, 100 MHz, acetone-d_6)	**HMP-P1 (10)** (^{13}C, 126 MHz, DMSO-d_6)[157]
206.5 (C15)	207.7
195.6 (C15')	196.8
183.8 (C4')	183.0
177.0 (C1')	177.1
161.7 (C17)	160.7
159.3 (C17')	157.7
152.7 (C3')	152.2
152.5 (C1)	151.0
152.4 (C6')	150.3
150.5 (C7')	148.9
148.3 (C3)	146.9
146.4 (C4)	144.9
145.1 (C7)	144.4
136.6 (C5)	134.3
126.4 (C16')	125.6
126.1 (C2')	125.5
117.2 (C5')	116.9
116.9 (C2)	115.8
114.5 (C18')	114.5
114.3 (C16)	113.8
113.0 (C6)	111.4
108.0 (C18)	107.2
87.2 (C12)	86.1
87.0 (C14')	83.4

[154] No ^{13}C NMR data for **10** was previously recorded according to a private communication with Prof. Y. Igarashi.

[155] Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 61–70.

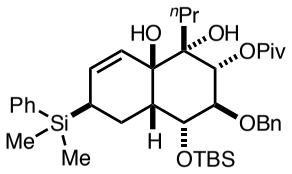
[156] The reference point for the residual carbon resonances of the NMR solvent were not listed.

[157] The ^{13}C NMR of **10** was taken in DMSO-d_6 due to low solubility in acetone-d_6 and CD_3OD.

Table S9. (continued)	
86.6 (C12')	79.3
83.9 (C13')	78.5
80.4 (C13)	77.3
78.8 (C14)	73.8
77.8 (C10')	72.8
77.0 (C10)	72.2
75.7 (C11')	69.52
71.6 (C11)	69.49
68.8 (C8')	66.9
62.6 (3-OMe)	62.2
62.0 (4-OMe)	61.6
56.2 (C9')	57.1
45.4 (C9)	46.4
37.3 (C19)	37.5
35.1 (C19')	34.9
29.6 (C8)	28.1
18.3 (C20)	17.7
17.1 (C20')	15.8
15.4 (C21)	15.3
15.1 (C21')	14.9

Appendix D

Chapter Four Catalog of CD, UV–Vis, ^{1}H and ^{13}C NMR Spectra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OH
OPiv
Ph
Si
Me
Me
H
OBn
OTBS

72

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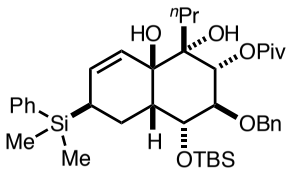
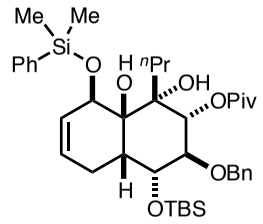
3.0
2.0
1.0
0
Chemical Shift (ppm)


HO
nPr
OH
OPiv
Ph
Si
Me
Me
H
OBn
OTBS

72

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
Me
Si
Ph
O
H
O
nPr
OH
OPiv
OBn
H
OTBS

74

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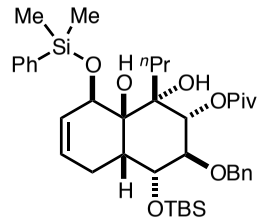
0
Chemical Shift (ppm)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Si
Ph
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H
O
nPr
OH
OPiv
OBn
H
OTBS

74

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180
170
160
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140
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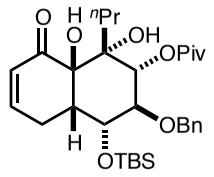
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)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nPr
OH
OPiv
OBn
H
OTBS

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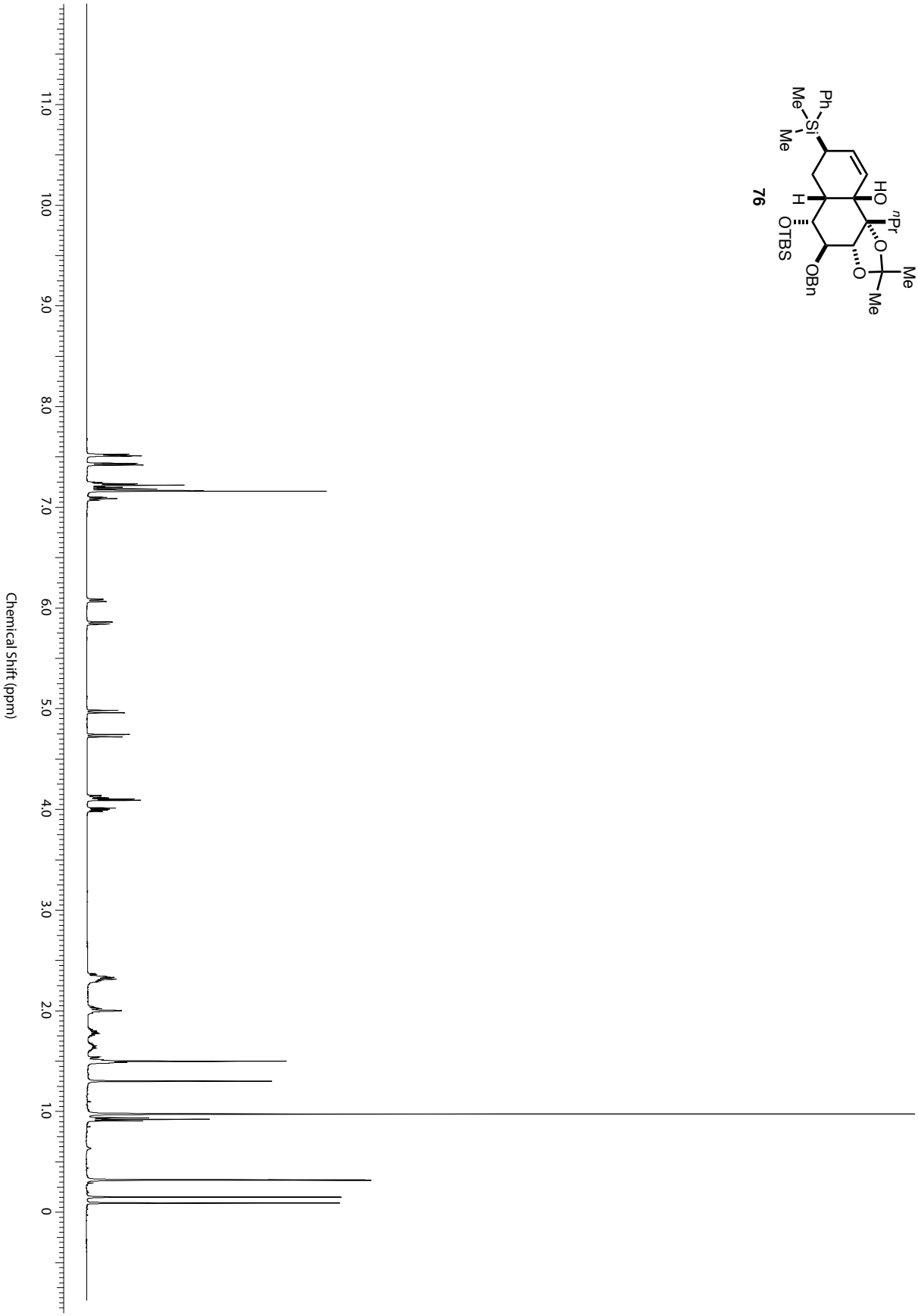
Chemical Shift (ppm)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Si
Me
HO
H
OTBS
nPr
O
O
Me
Me
OBn
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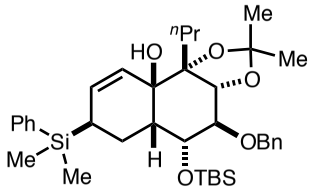
0
Chemical Shift (ppm)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HO
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Me
O
Ph
Si
Me
Me
H
OBn
OTBS

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200
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110
100
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80
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30
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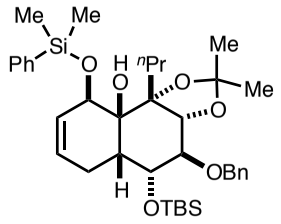
Chemical Shift (ppm)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OBn
H
OTBS

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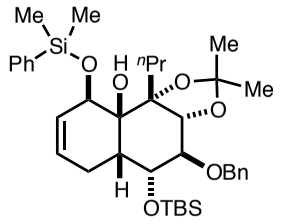
Chemical Shift (ppm)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H
OTBS

77

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180
170
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30
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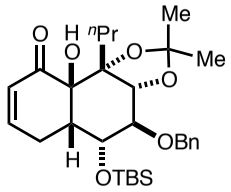
Chemical Shift (ppm)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OBn
H
OTBS

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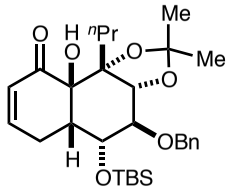
Chemical Shift (ppm)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nPr
O
Me
Me
O
OBn
H
OTBS

78

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180
170
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110
100
90
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50
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30
20
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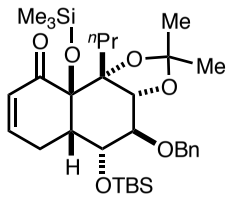
0
-10
Chemical Shift (ppm)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Me
O
OBn
H
OTBS

ent-**63**

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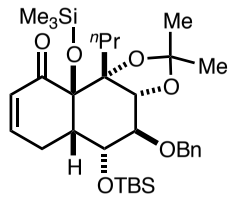
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O
nPr
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Me
Me
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OBn
H
OTBS

ent-**63**

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180
170
160
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100
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50
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30
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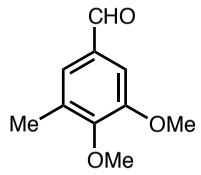
-10
Chemical Shift (ppm)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OMe
OMe

S3

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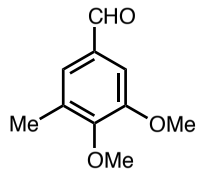
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OMe
OMe

S3

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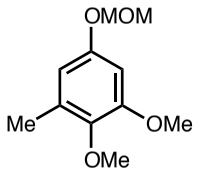
Chemical Shift (ppm)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OMe
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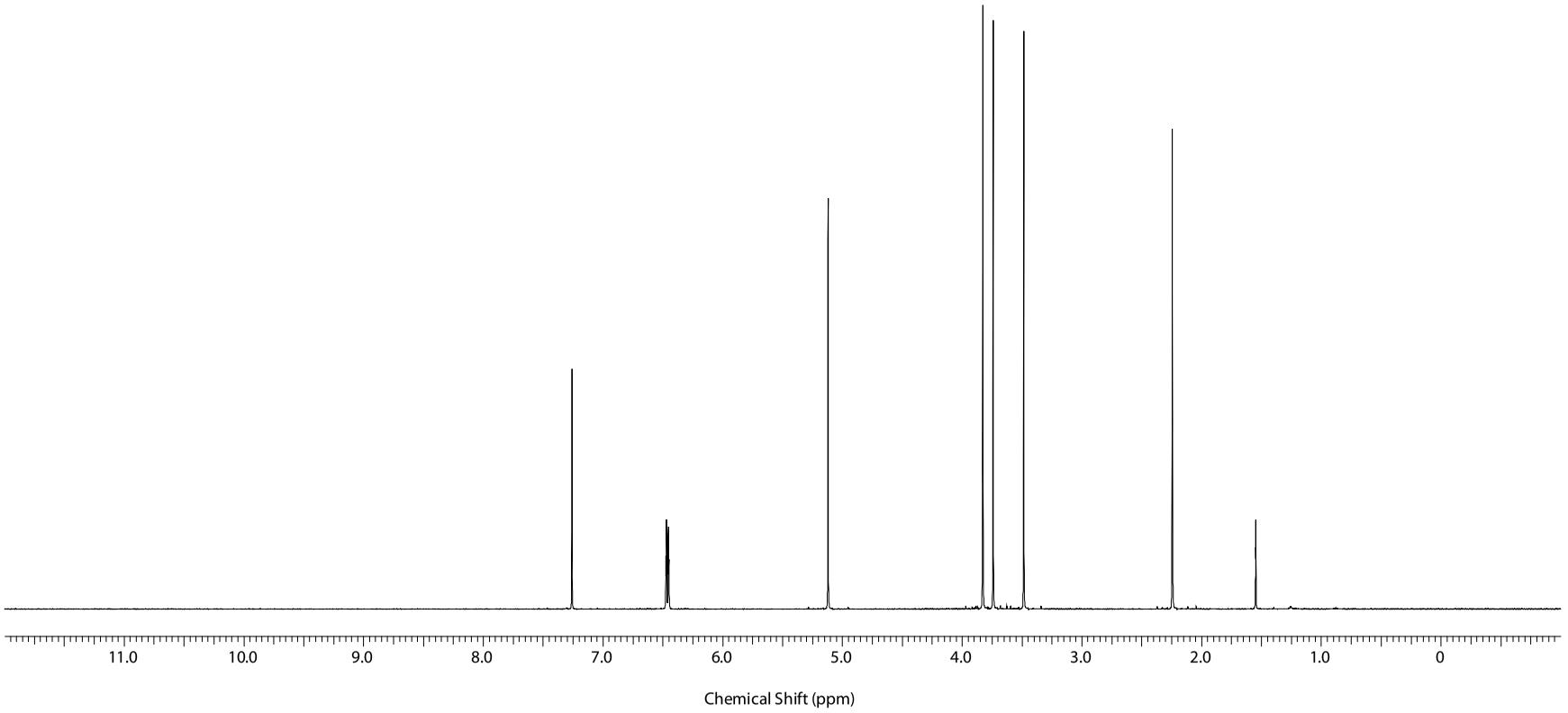
34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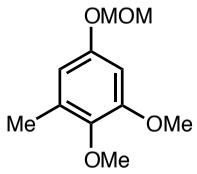
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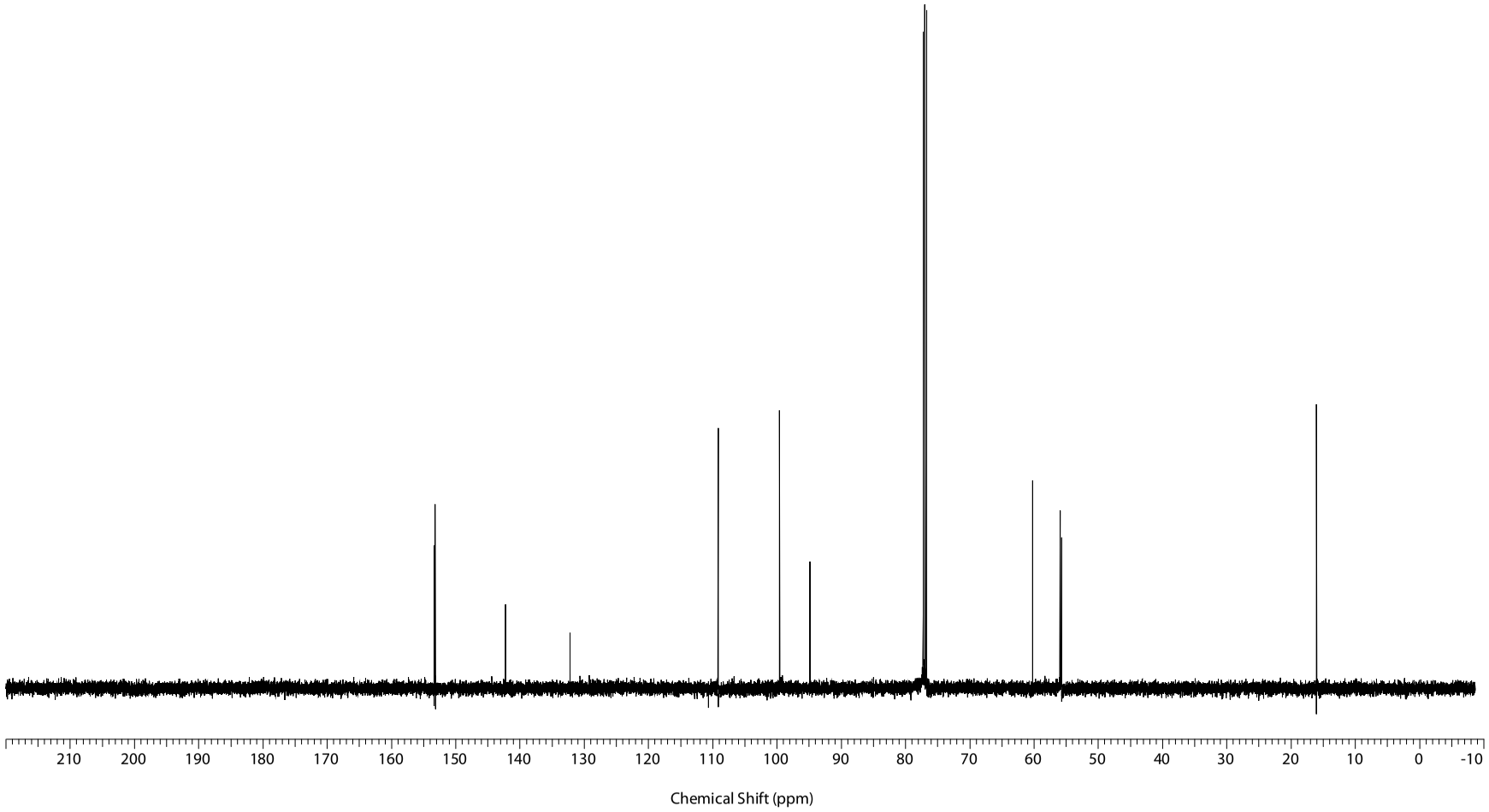
OMe
OMe

34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100
90
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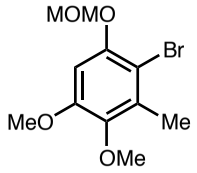
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
Br
MeO
Me
OMe

S5

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3.0
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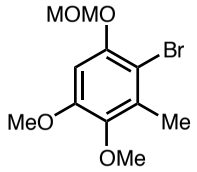
Chemical Shift (ppm)


MOMO
Br
MeO
Me
OMe

S5

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100
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80
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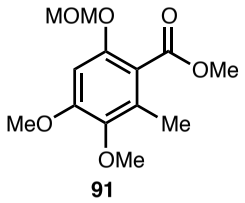
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
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OMe
MeO
Me
OMe

91

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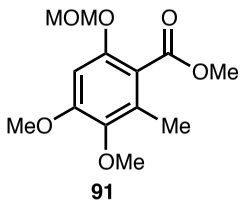
Chemical Shift (ppm)


MOMO
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OMe
MeO
Me
OMe

91

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180
170
160
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140
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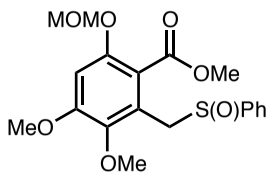
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
OMe
S(O)Ph
MeO
OMe

97

11.0
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7.0
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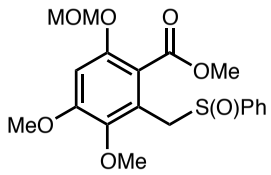
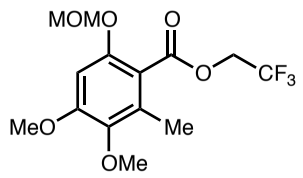
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
OMe
S(O)Ph
MeO
OMe

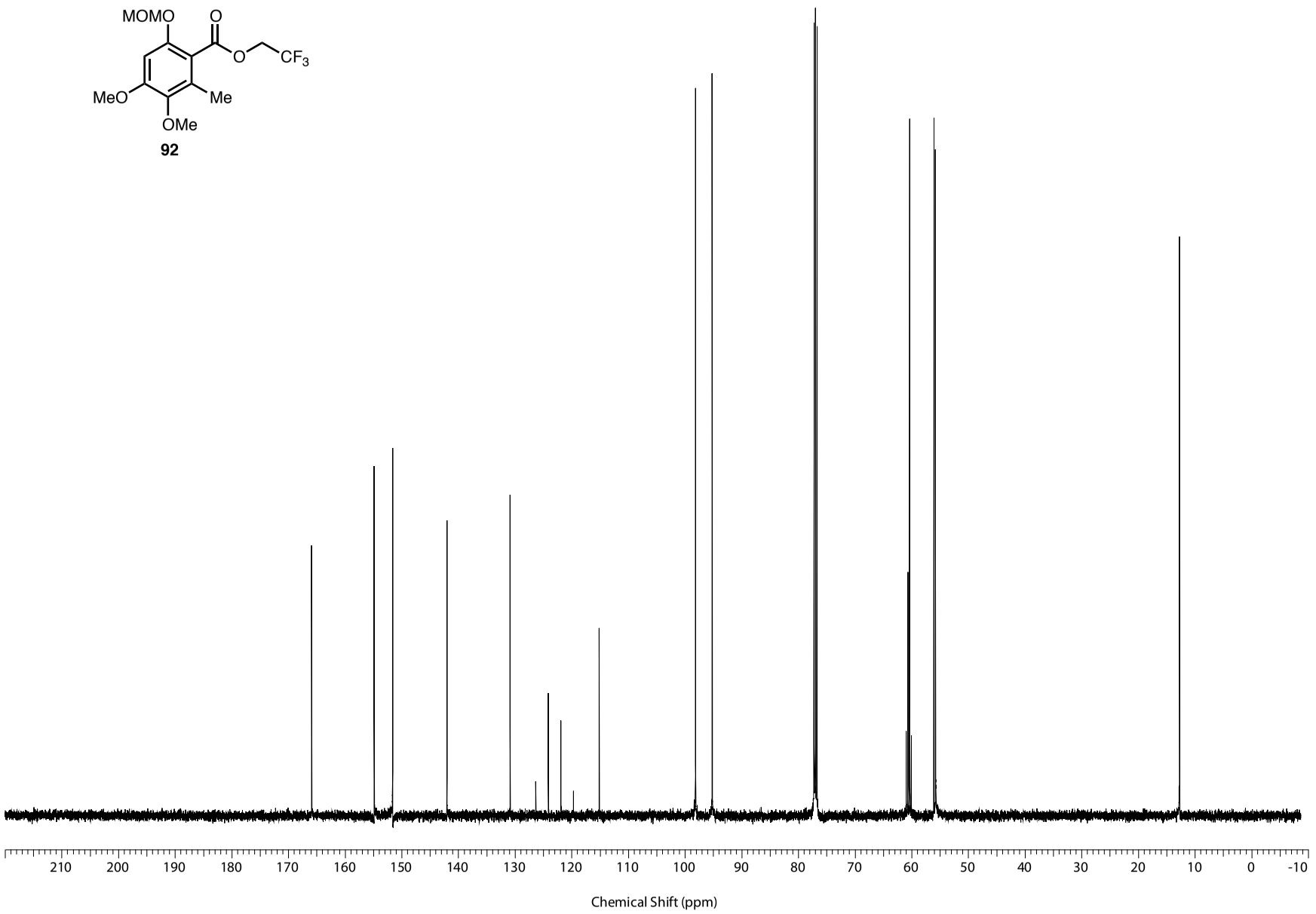
97

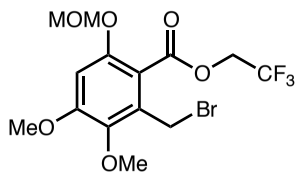
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
O
CF3
MeO
Me
OMe

92

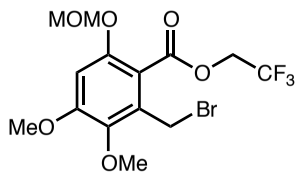
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
O
CF3
MeO
Me
OMe
92
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
O
CF3
Br
MeO
OMe

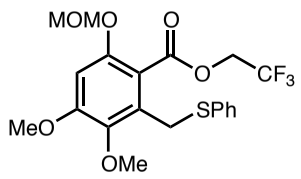
94

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
O
CF3
Br
MeO
OMe

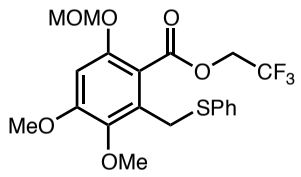
94

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
O
CF3
SPh
MeO
OMe

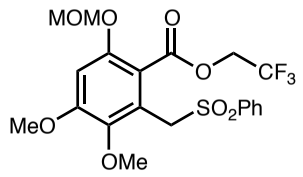
96

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
O
CF3
SPh
MeO
OMe

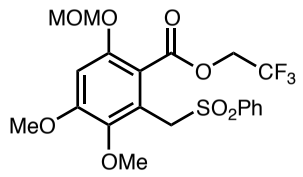
96

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
O
CF3
SO2Ph
MeO
OMe

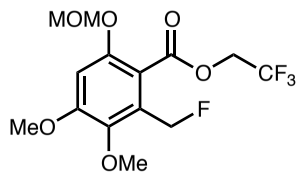
98

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
O
CF3
SO2Ph
MeO
OMe

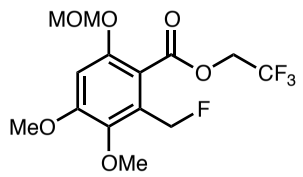
98

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
O
O
CF3
F
MeO
OMe

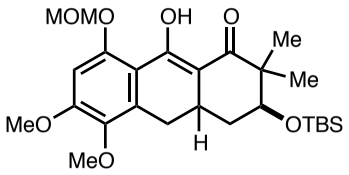
99

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
O
O
CF3
F
MeO
OMe

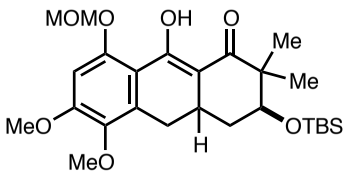
99

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
OH
O
Me
Me
MeO
OTBS
H
MeO

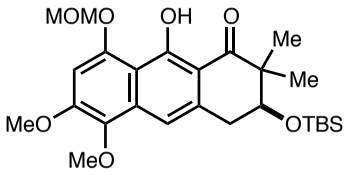
101

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
OH
O
Me
Me
MeO
OTBS
H
MeO

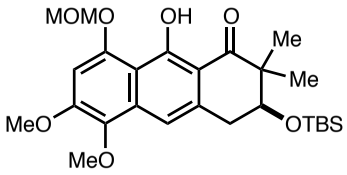
101

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
OH
O
Me
Me
MeO
OTBS
MeO

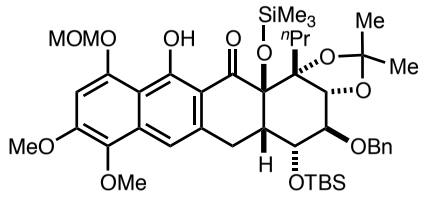
102

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MOMO
OH
O
Me
Me
MeO
OTBS
MeO

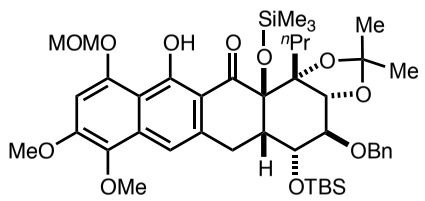
102

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MOMO
OH
O
SiMe3
O
nPr
O
Me
Me
O
MeO
OBn
H
OMe
OTBS

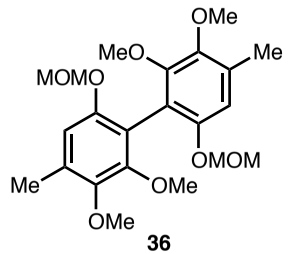
89

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

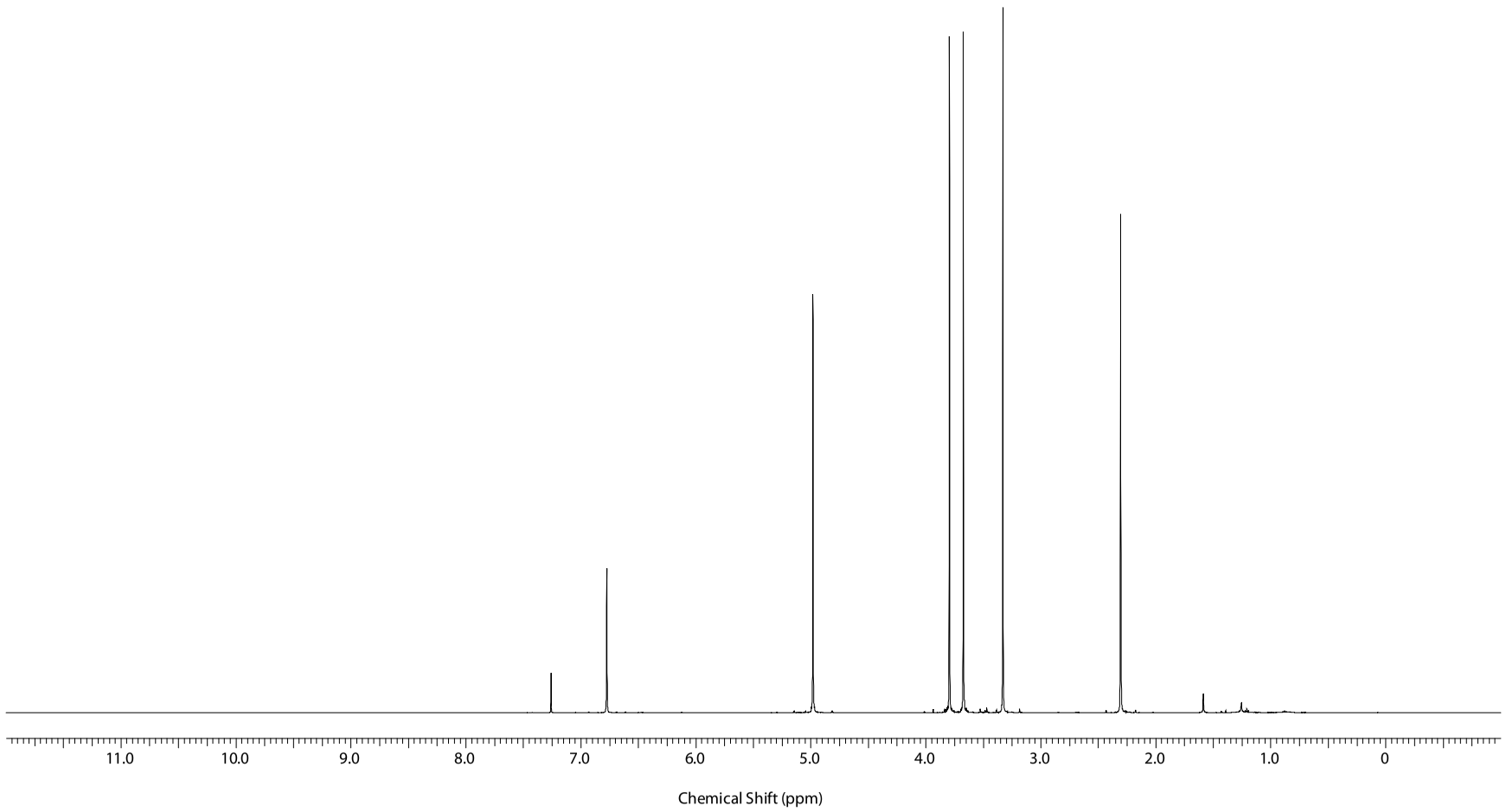

MOMO
OH
O
SiMe3
O
nPr
O
Me
Me
O
MeO
OBn
H
OMe
OTBS

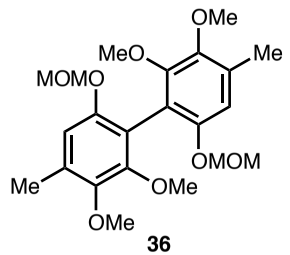
89

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

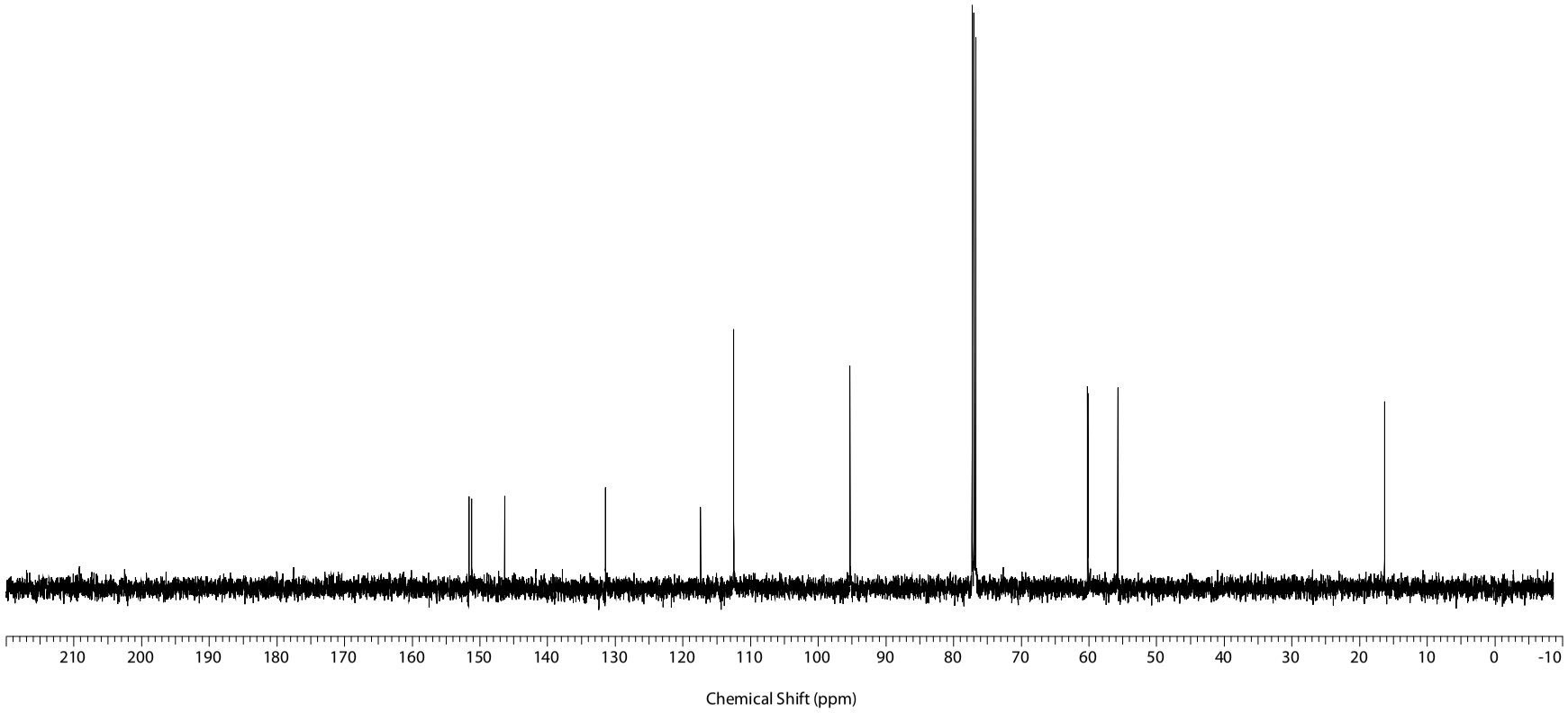

OMe
MeO
Me
MOMO
OMOM
Me
OMe
OMe

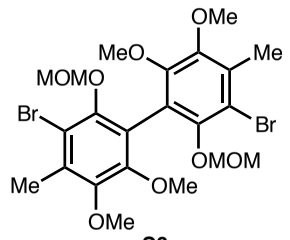
36


11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

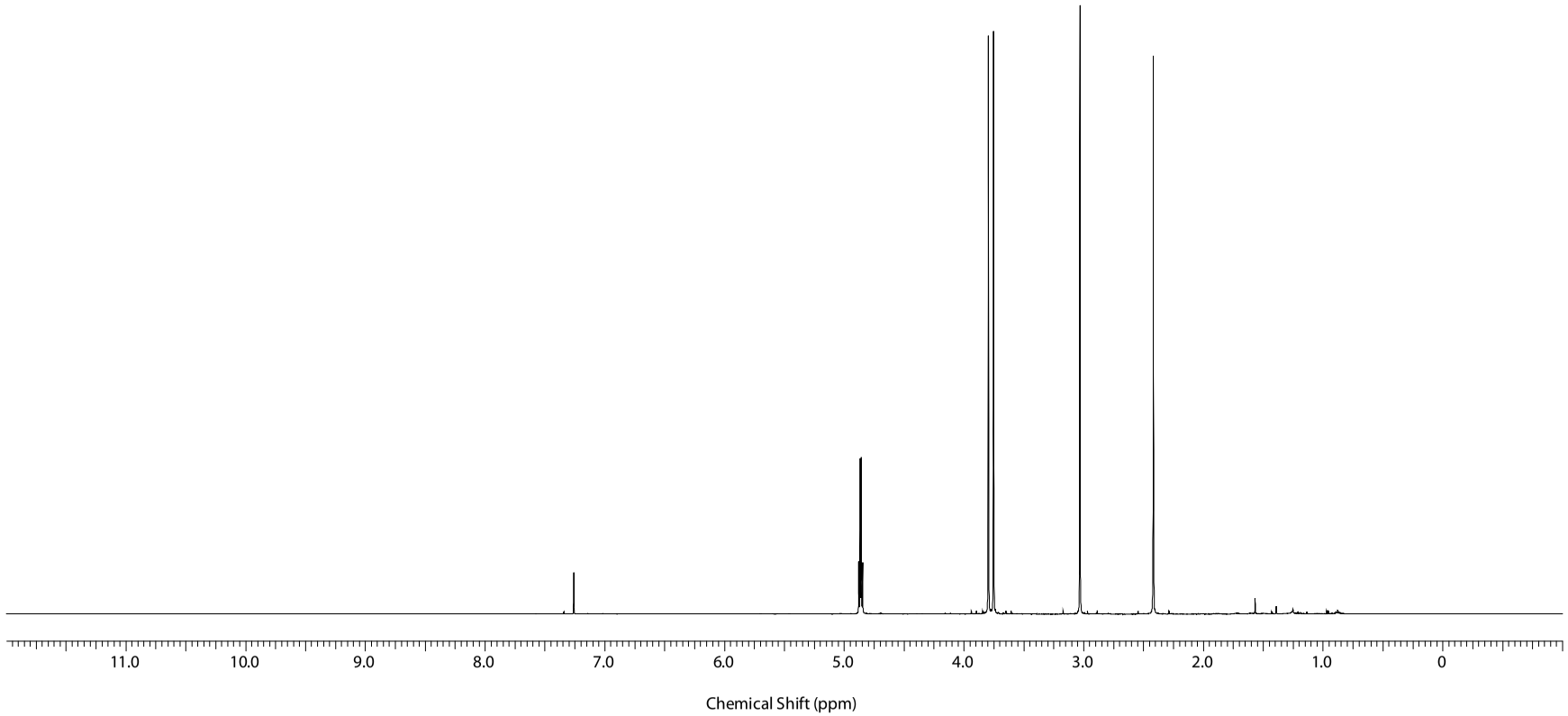

OMe
MeO
Me
MOMO
OMOM
Me
OMe
OMe

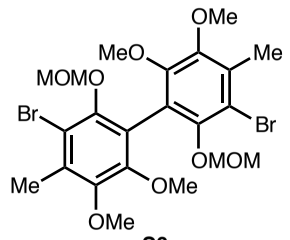
36


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

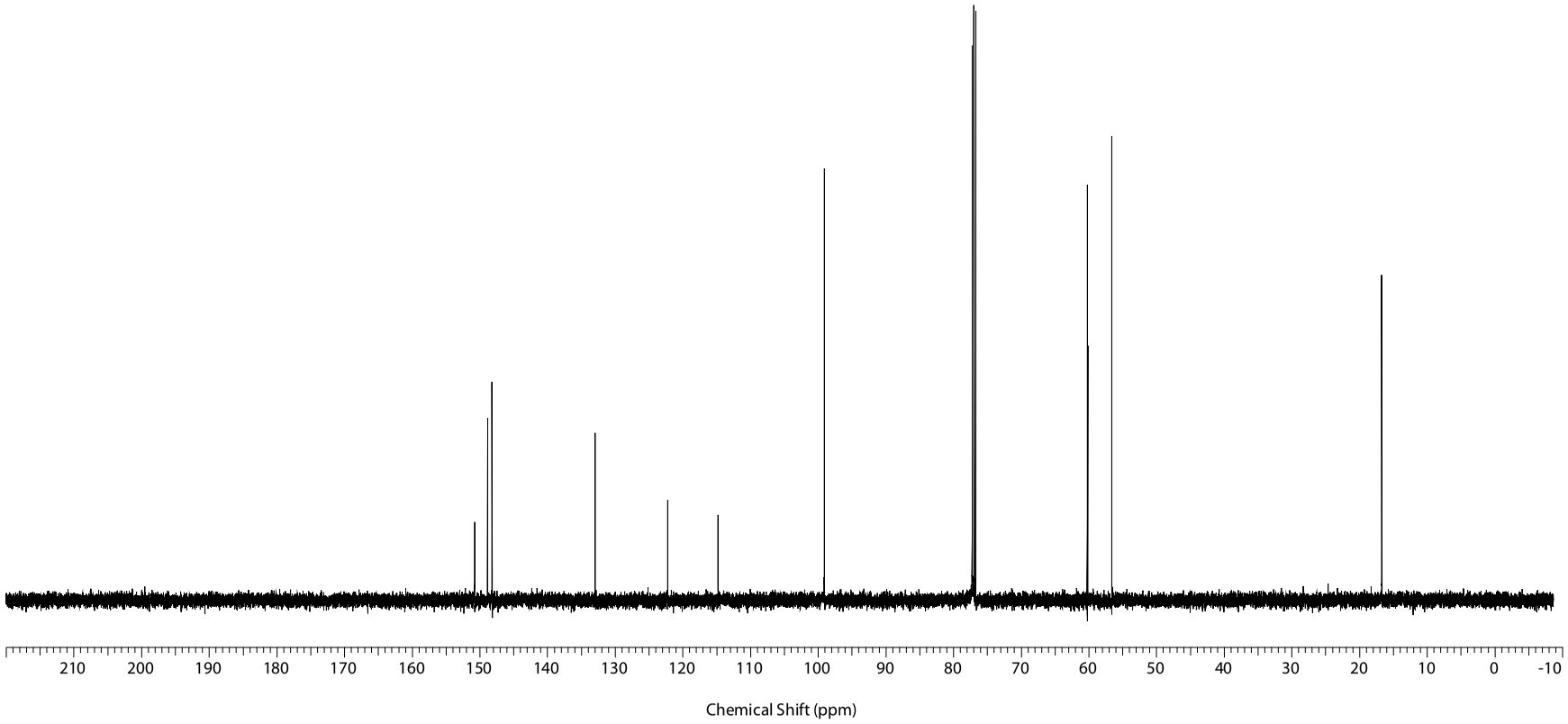

OMe
MeO
Me
MOMO
Br
Br
OMOM
Me
OMe
OMe

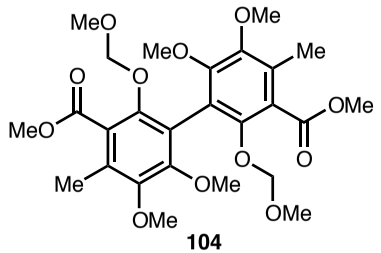
S6


11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

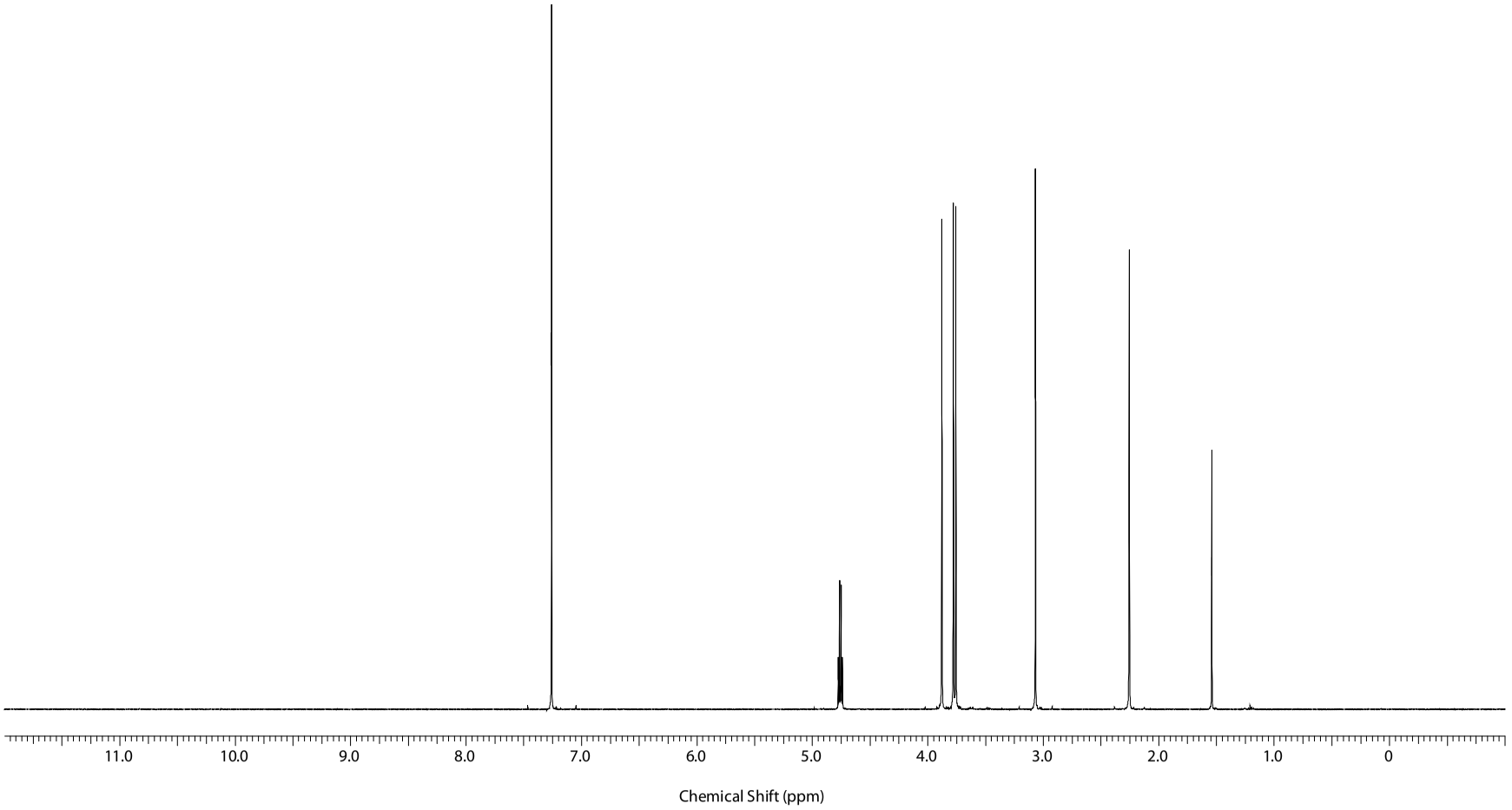

OMe
MeO
Me
MOMO
Br
Br
OMOM
Me
OMe
OMe

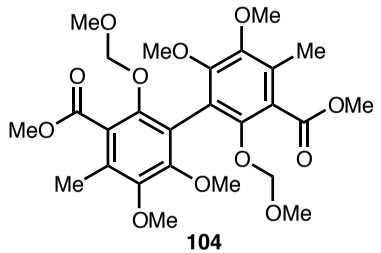
S6


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

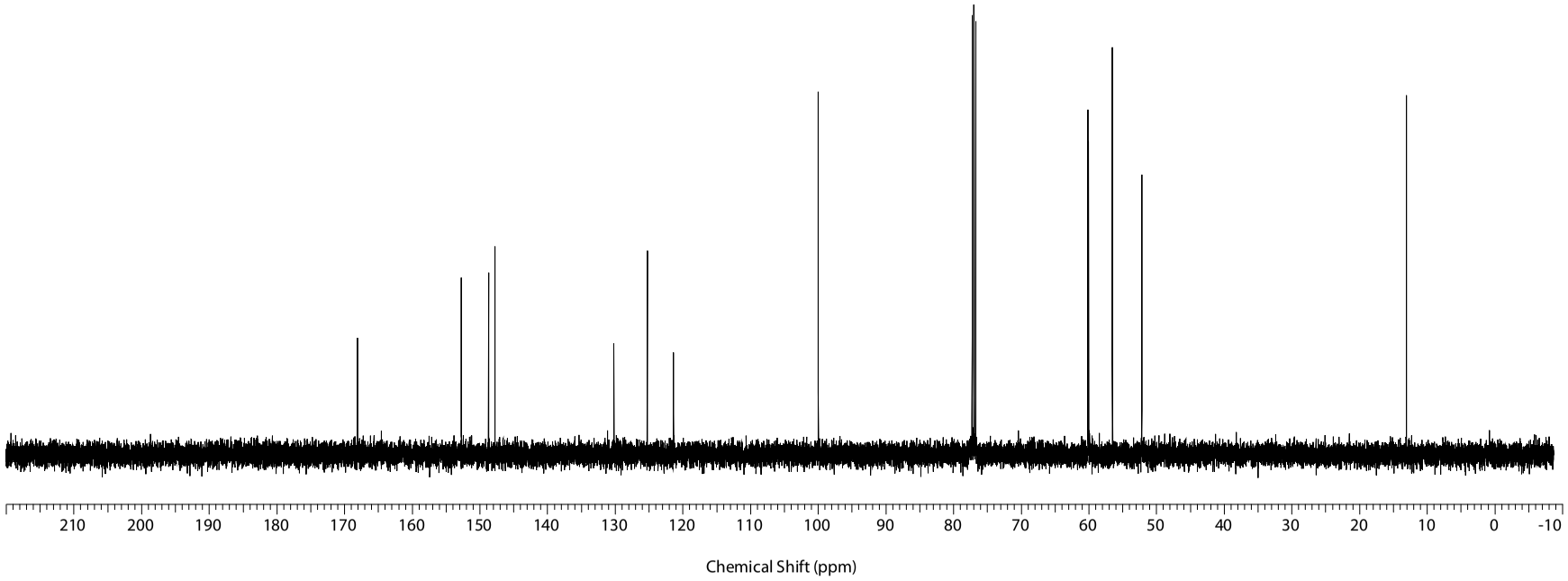

MeO
OMe
MeO
Me
O
O
OMe
MeO
O
O
Me
OMe
OMe
OMe

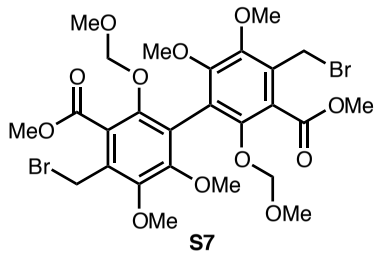
104


11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

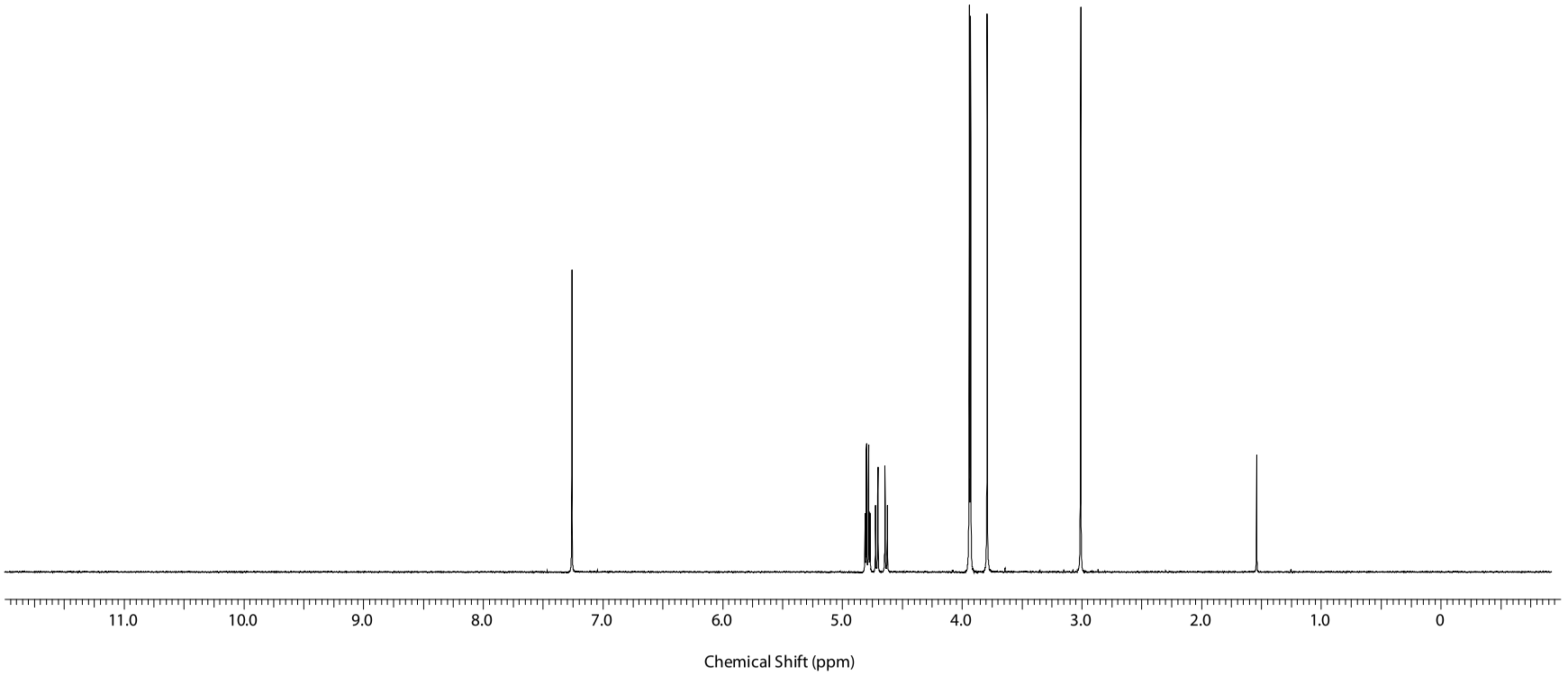

MeO
OMe
MeO
Me
O
O
OMe
MeO
O
O
Me
OMe
OMe
OMe

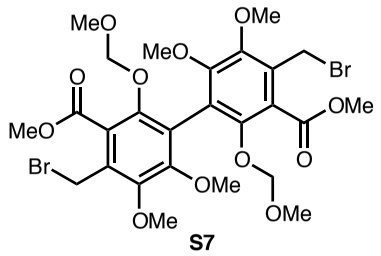
104


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MeO
OMe
MeO
Br
O
O
OMe
MeO
O
O
Br
O
OMe
OMe
OMe

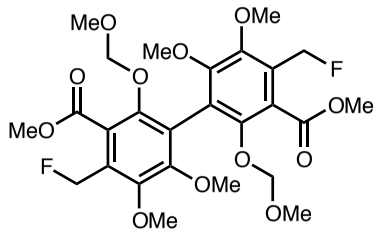
S7


11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MeO
OMe
MeO
Br
O
O
OMe
MeO
O
O
Br
OMe
OMe
OMe

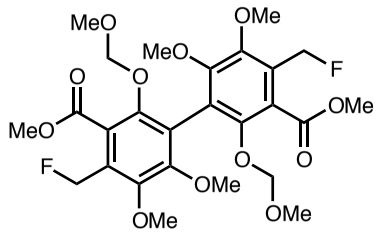
S7

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

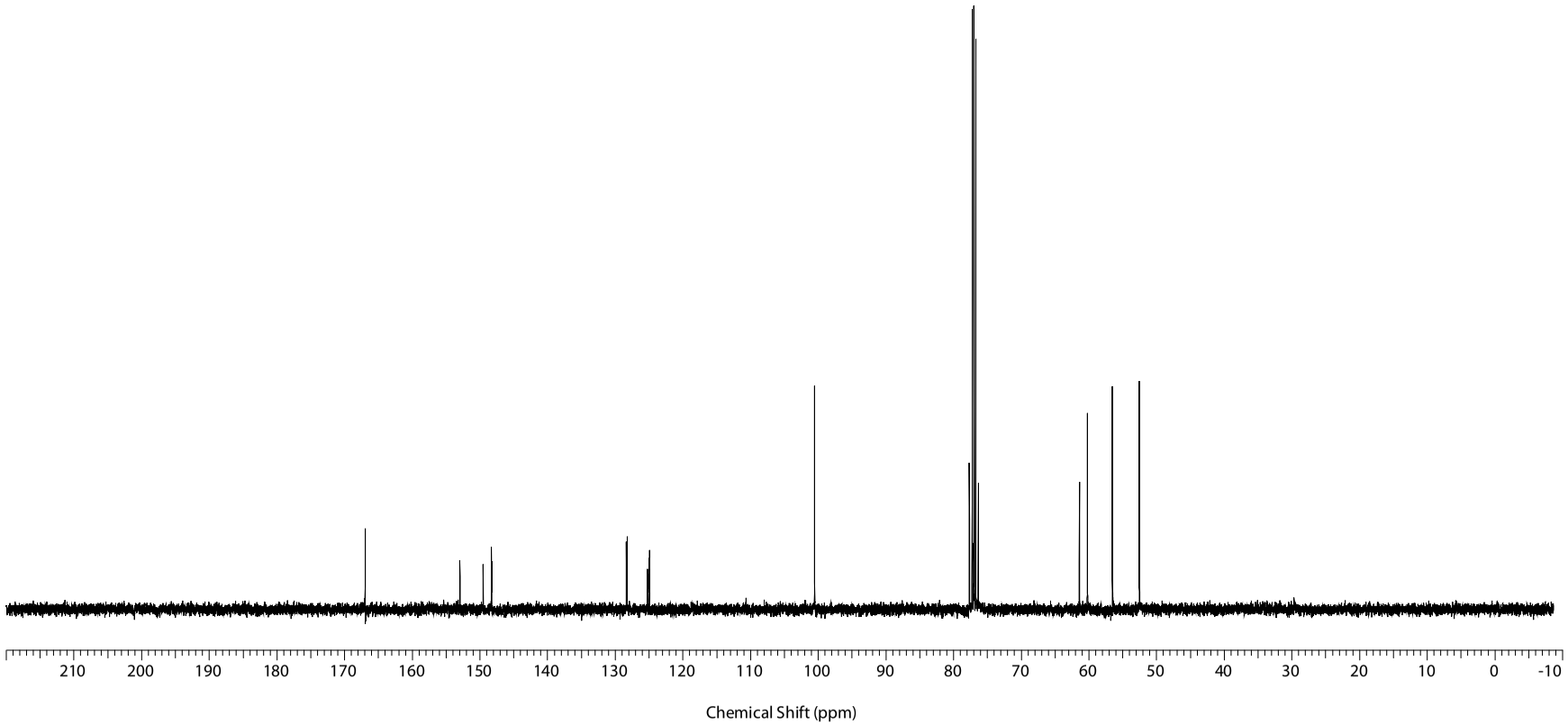

MeO
OMe
MeO
F
O
O
OMe
MeO
O
O
F
OMe
OMe
OMe

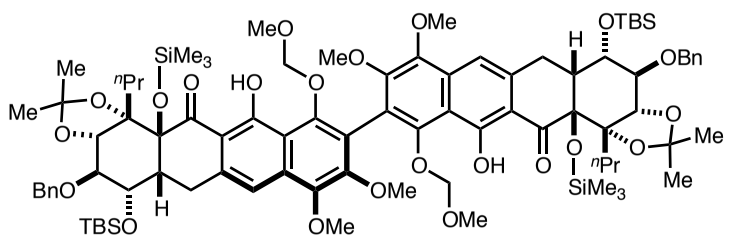
108

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MeO
OMe
MeO
F
O
O
OMe
MeO
O
O
F
OMe
OMe
OMe

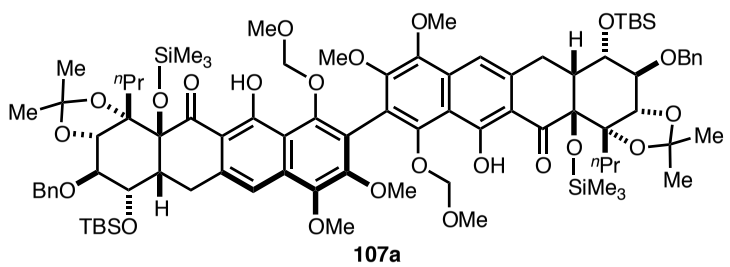
108


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MeO
OMe
OTBS
SiMe3
MeO
H
OBn
Me
nPr
HO
O
O
O
Me
O
O
O
O
Me
OH
O
O
nPr
BnO
OMe
SiMe3
Me
H
TBSO
OMe
OMe

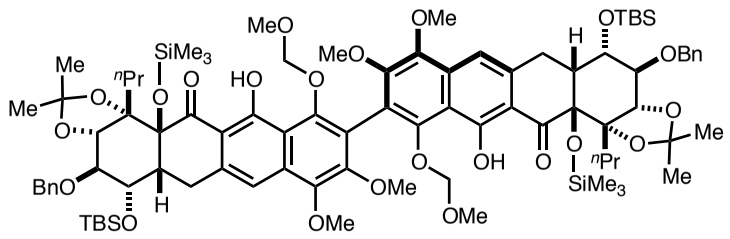
107a

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)


MeO
OMe
OTBS
SiMe3
MeO
H
OBn
Me
nPr
HO
O
O
O
Me
O
O
O
O
Me
OH
O
nPr
BnO
OMe
SiMe3
Me
H
TBSO
OMe
OMe

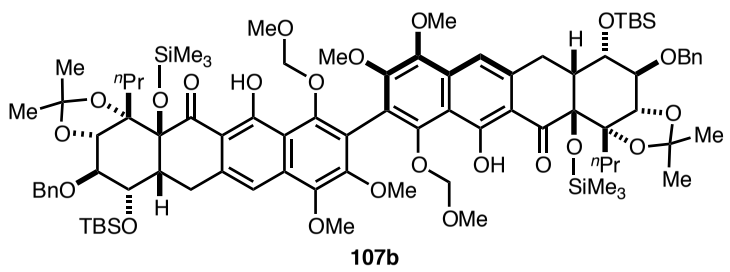
107a

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MeO
OMe
OTBS
SiMe3
MeO
H
OBn
Me
nPr
HO
O
O
O
O
O
Me
O
O
O
Me
BnO
OMe
OH
O
nPr
SiMe3
H
TBSO
OMe
OMe

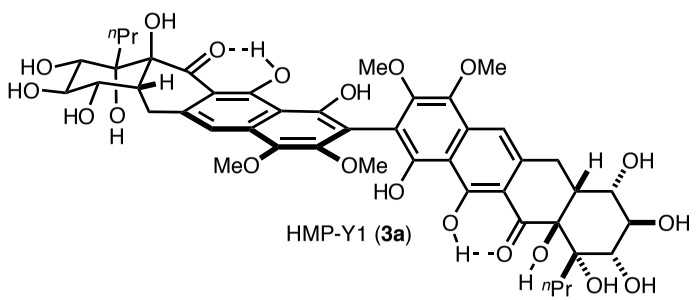
107b

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

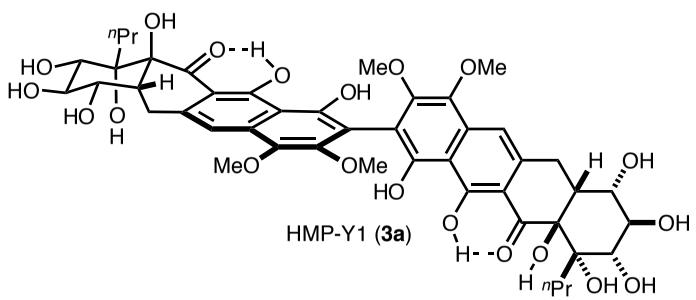

MeO
OMe
OTBS
MeO
SiMe3
H
OBn
Me
nPr
HO
O
O
O
O
O
Me
O
O
O
O
Me
OH
O
O
nPr
BnO
OMe
O
SiMe3
Me
H
TBSO
OMe
OMe

107b

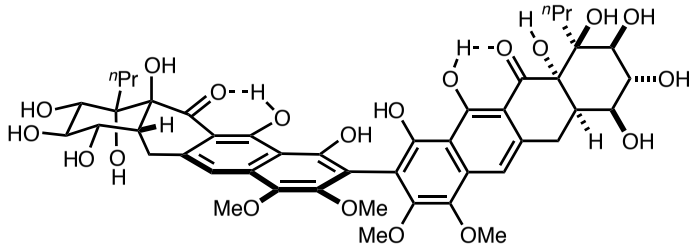
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


HMP-Y1 (3a)

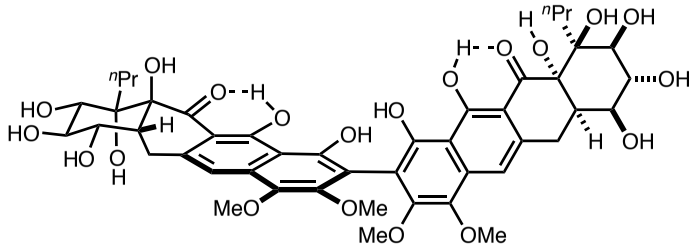
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


HMP-Y1 (3a)

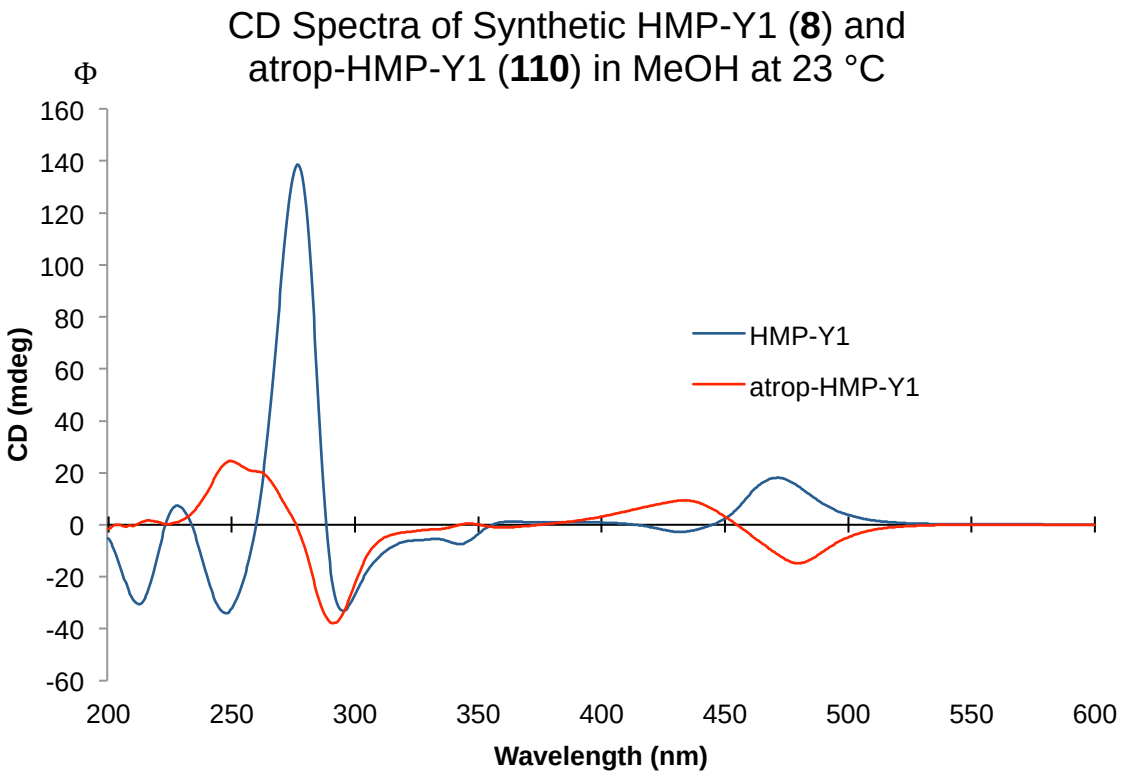
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

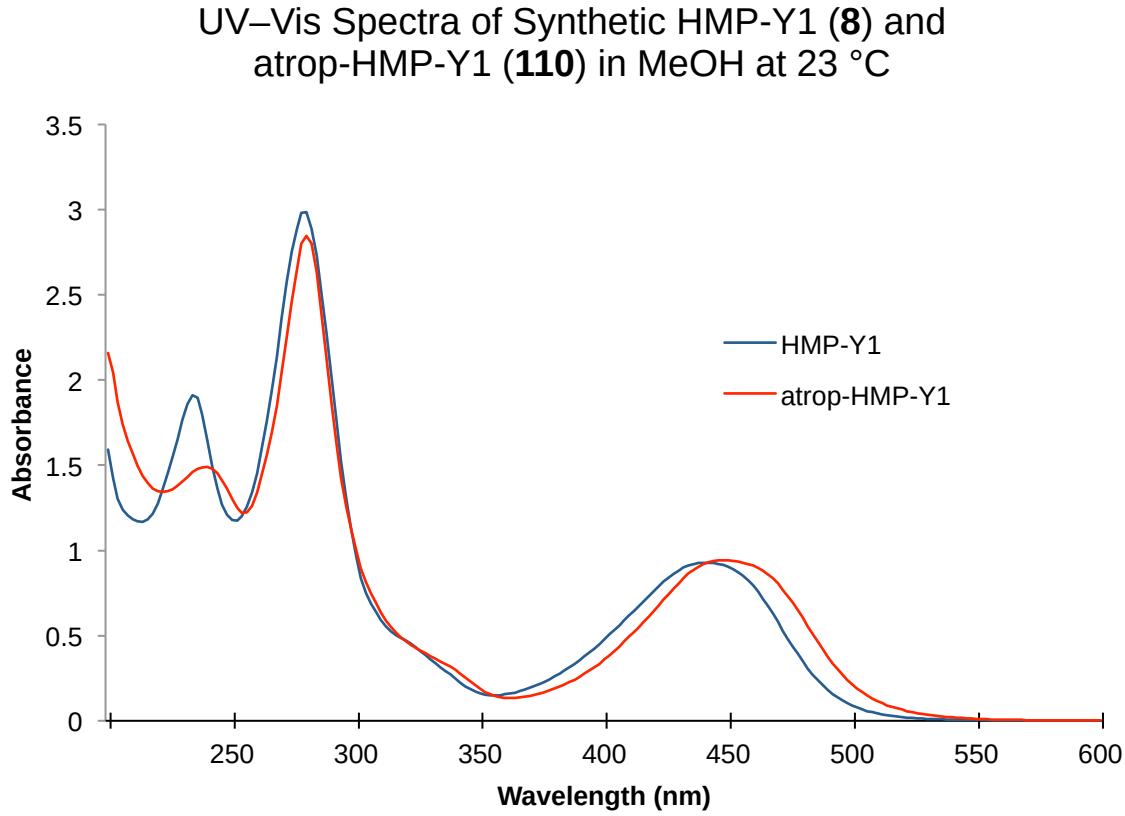


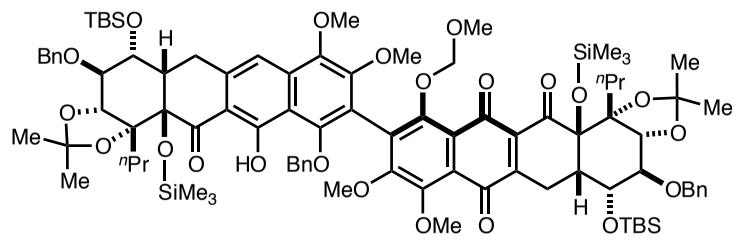
atrop-HMP-Y1 (**110**)



atrop-HMP-Y1 (**110**)

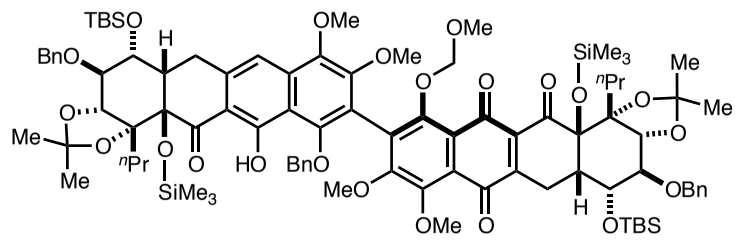

CD Spectra of Synthetic HMP-Y1 (8) and atrop-HMP-Y1 (110) in MeOH at 23 °C
Φ
160
140
120
100
80
60
40
20
0
-20
-40
-60
CD (mdeg)
200
250
300
350
400
450
500
550
600
Wavelength (nm)
HMP-Y1
atrop-HMP-Y1


UV–Vis Spectra of Synthetic HMP-Y1 (8) and atrop-HMP-Y1 (110) in MeOH at 23 °C
3.5
3
2.5
2
1.5
1
0.5
0
Absorbance
250
300
350
400
450
500
550
600
Wavelength (nm)
HMP-Y1
atrop-HMP-Y1


TBSO
H
OMe
OMe
OMe
BnO
SiMe3
Me
nPr
O
Me
Me
O
O
O
O
O
O
O
O
nPr
O
Me
O
SiMe3
O
HO
BnO
MeO
OMe
O
H
OBn
OTBS

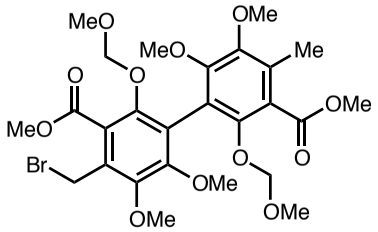
111

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

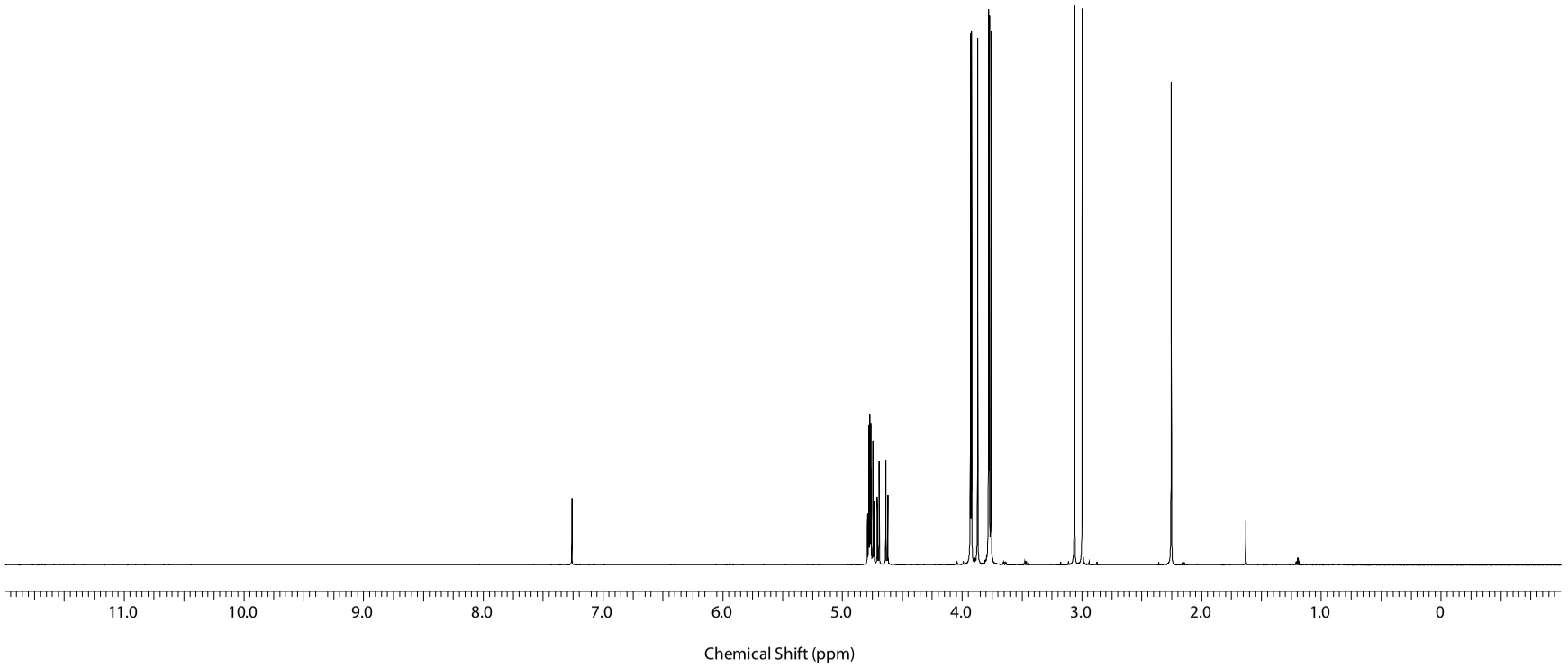

TBSO
H
OMe
OMe
OMe
BnO
SiMe3
Me
nPr
O
Me
O
Me
O
nPr
O
O
HO
BnO
O
O
O
O
O
O
O
SiMe3
MeO
OMe
O
H
OBn
OTBS

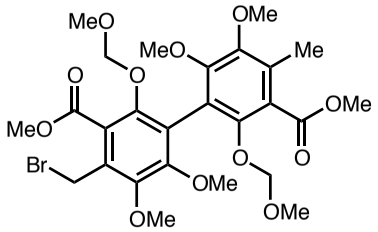
111

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

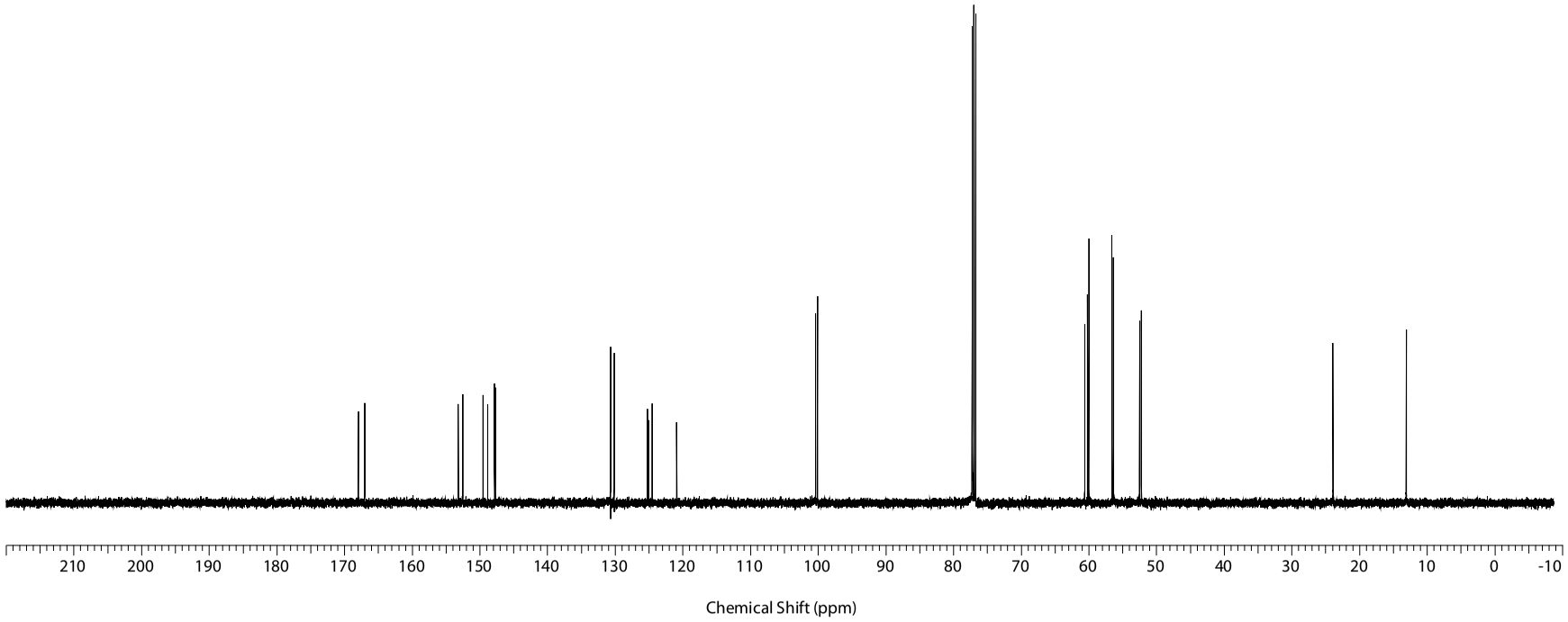

MeO
OMe
MeO
Me
O
O
OMe
MeO
O
Br
OMe
OMe
OMe

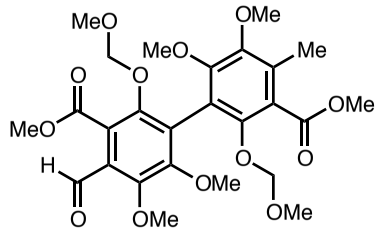
115


11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

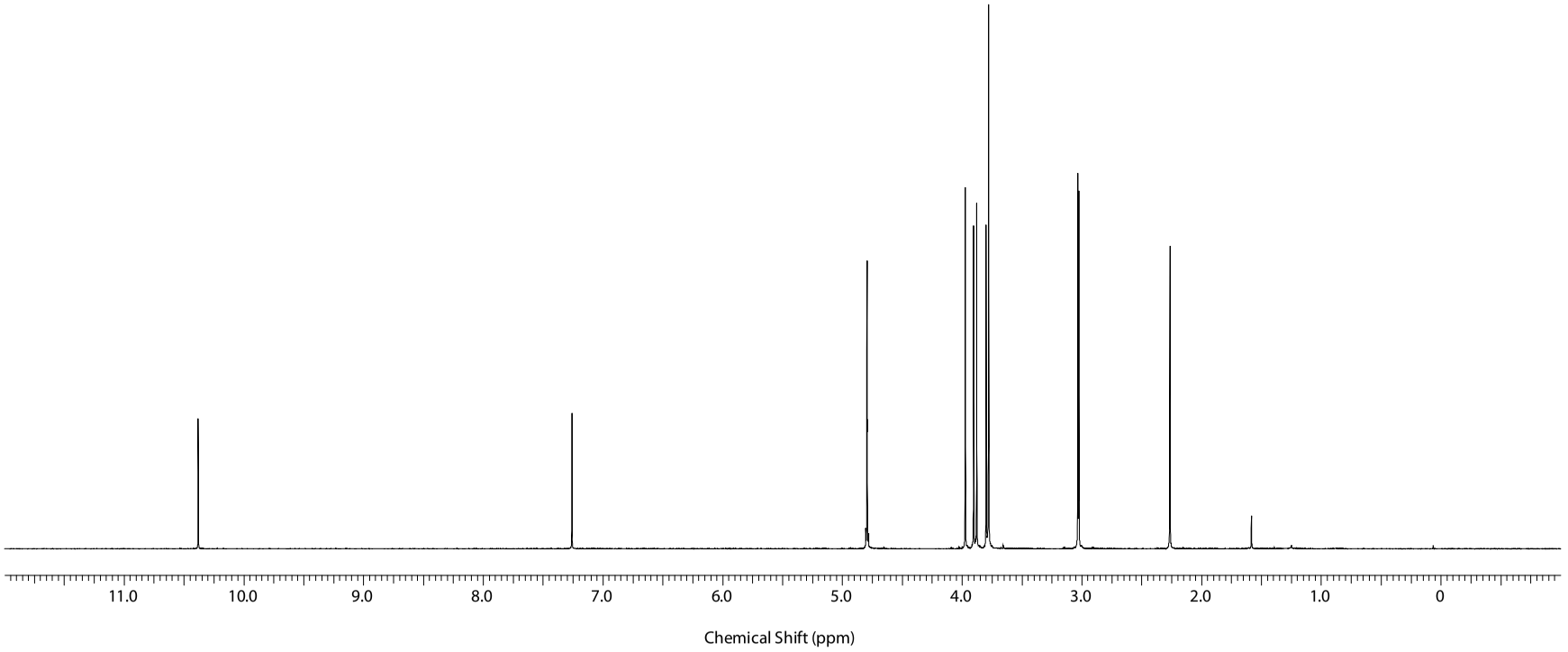

MeO
OMe
MeO
Me
O
O
OMe
MeO
O
Br
OMe
OMe
OMe

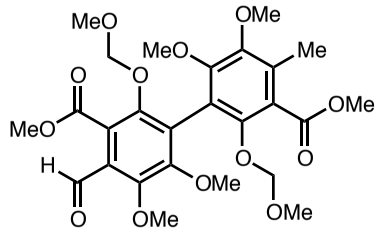
115


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MeO
OMe
MeO
Me
O
O
OMe
MeO
O
H
OMe
O
OMe
OMe
O
OMe

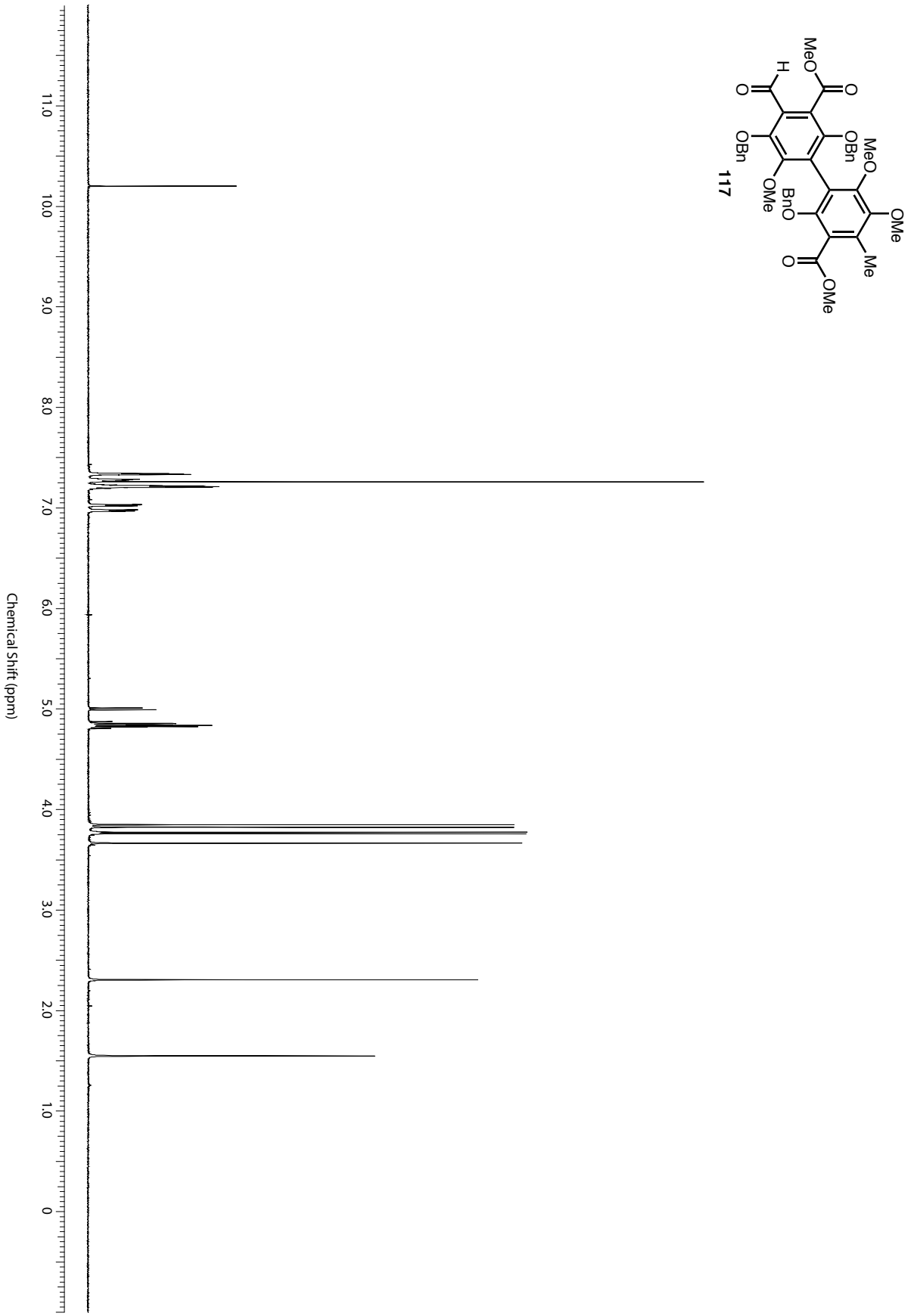
116

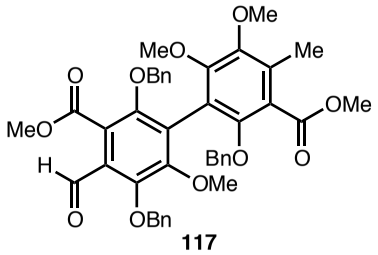

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


MeO
OMe
MeO
Me
O
O
OMe
MeO
O
O
H
OMe
O
OMe
OMe

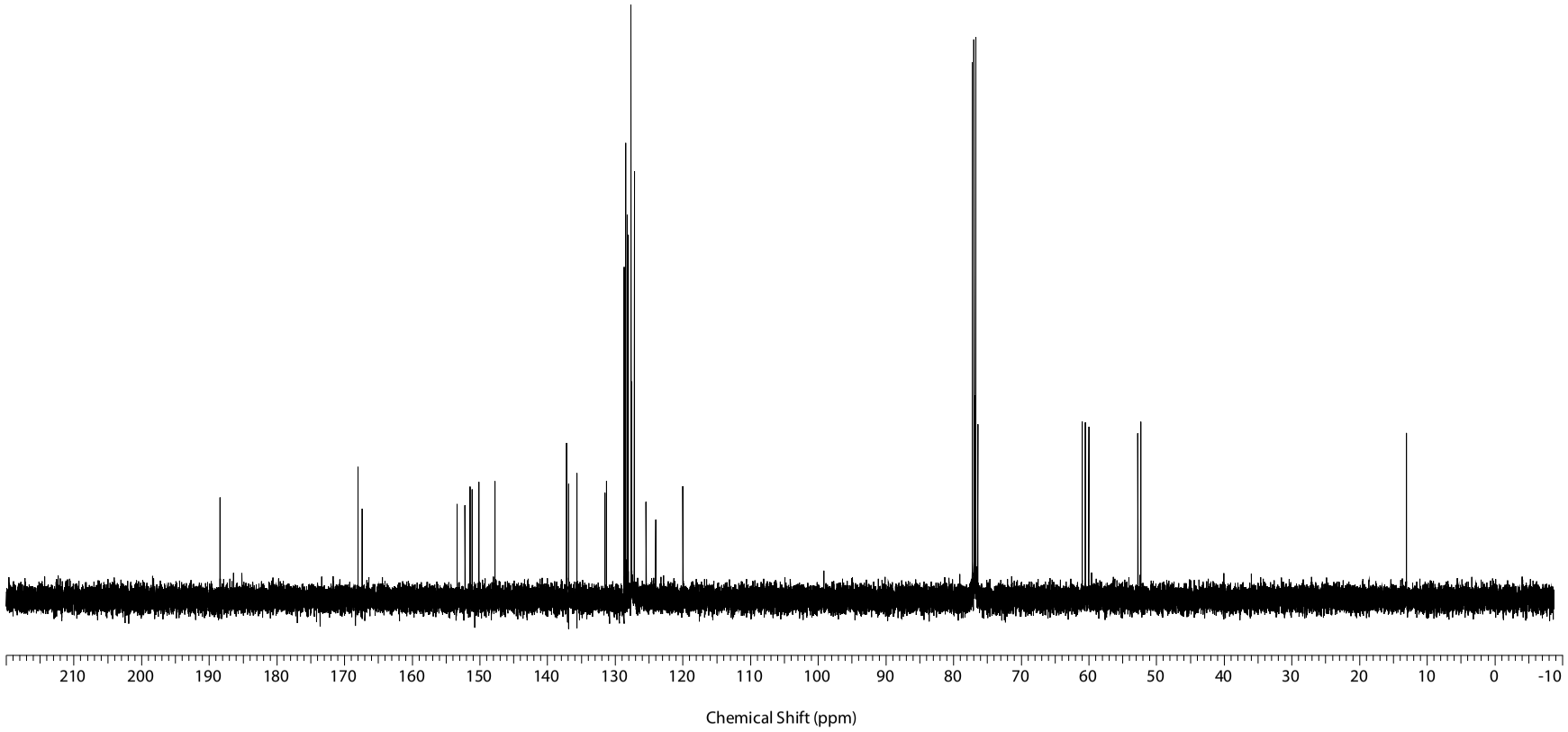
116

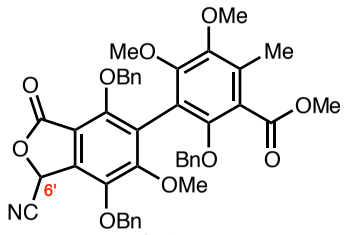
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


MeO
O
H
O
OBn
OBn
MeO
OBn
BnO
OMe
OMe
Me
O
OMe
117
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


OMe
MeO
Me
O
OBn
OMe
MeO
BnO
O
H
OMe
O
OBn

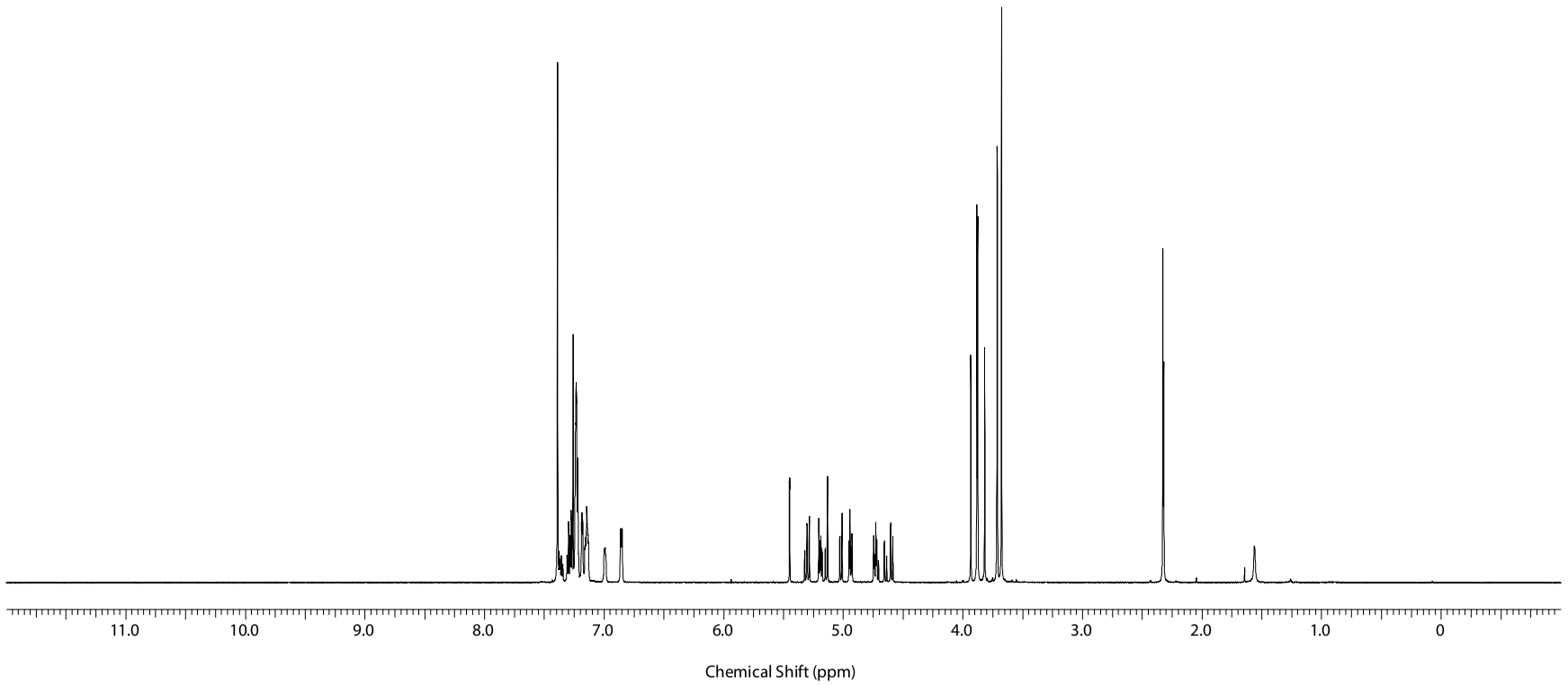
117

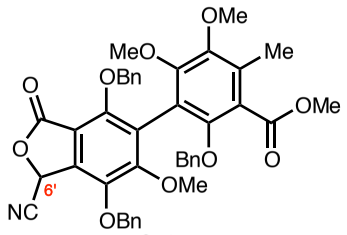

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



S12

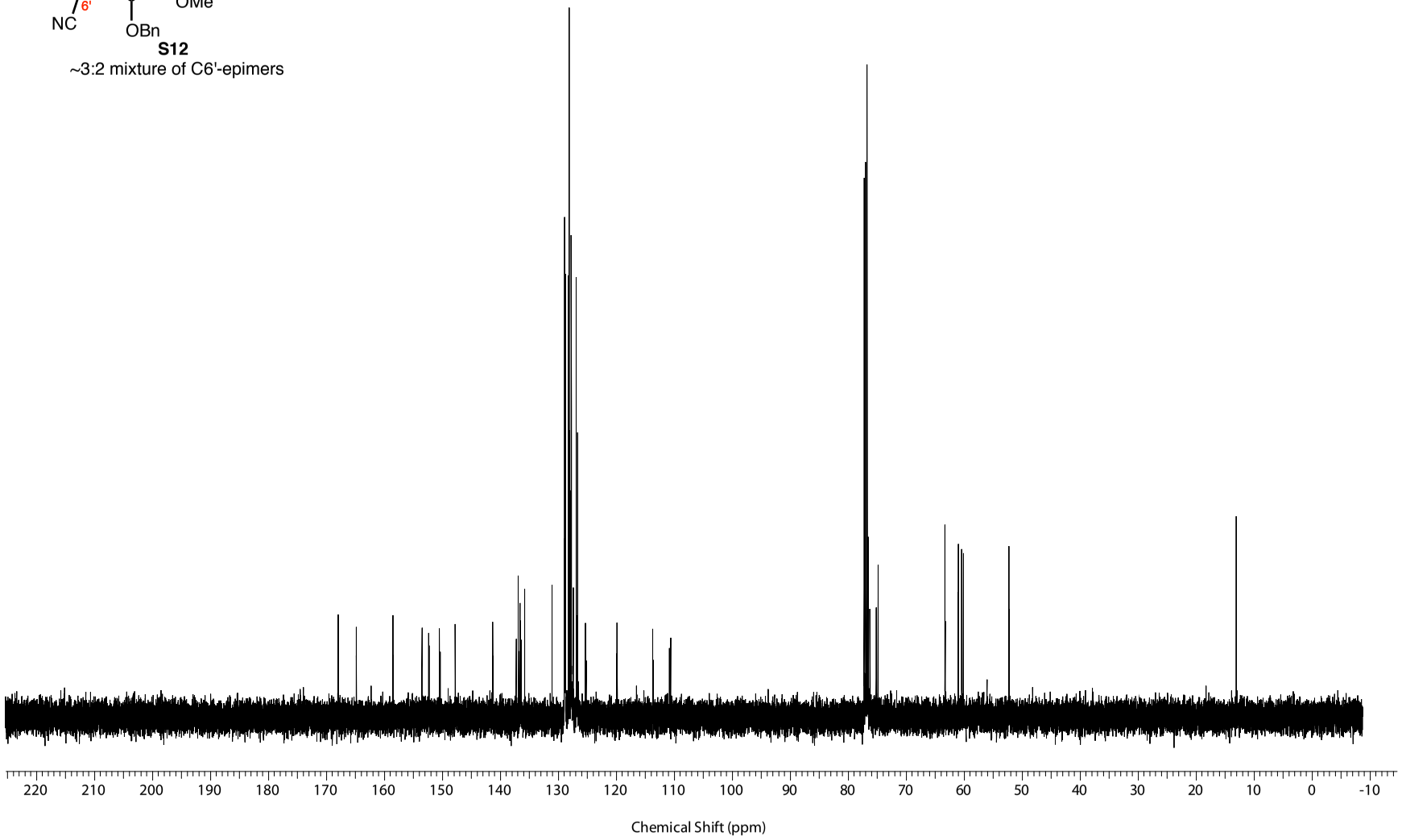
~3:2 mixture of C6'-epimers

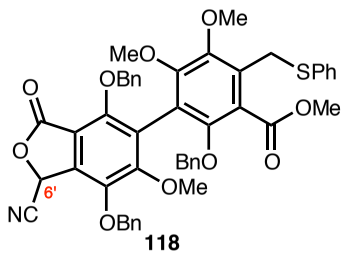




S12

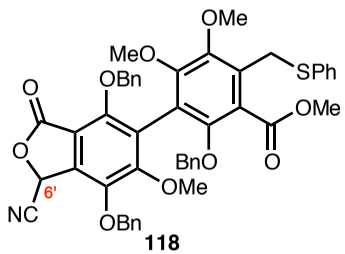
~3:2 mixture of C6'-epimers





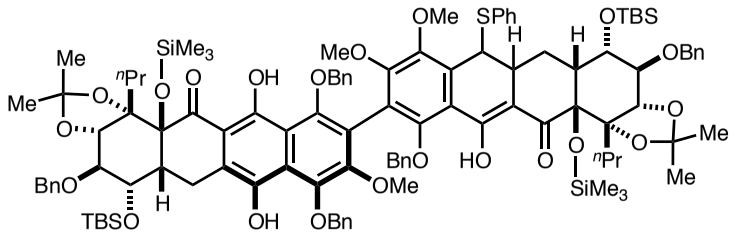
118

~2:1 mixture of C6'-epimers



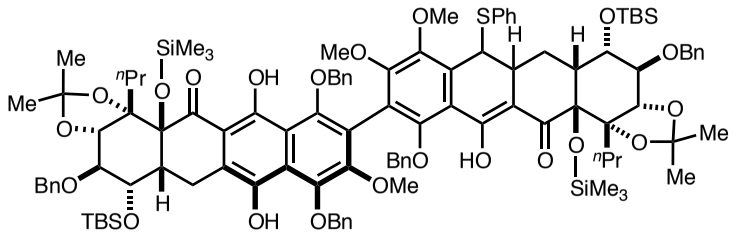
118

~2:1 mixture of C6'-epimers


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
SPh
H
H
OTBS
OBn
O
O
Me
Me
BnO
TBSO
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3

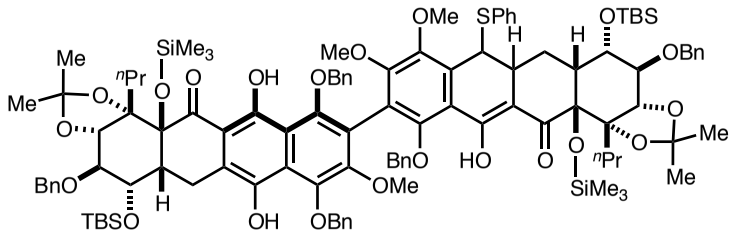
128a

17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
SPh
H
H
OTBS
OBn
O
O
Me
Me
BnO
HO
O
O
nPr
SiMe3
BnO
OMe
TBSO
H
OH
OBn

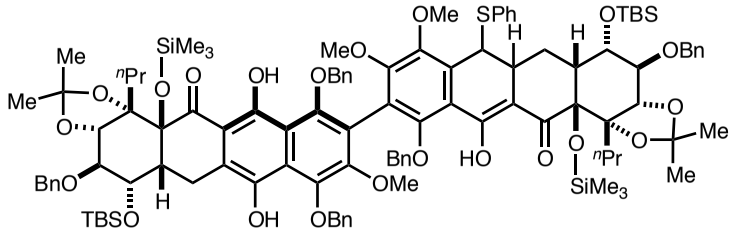
128a

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
SPh
H
H
OTBS
OBn
BnO
TBSO
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3
O
O
Me
Me

128b

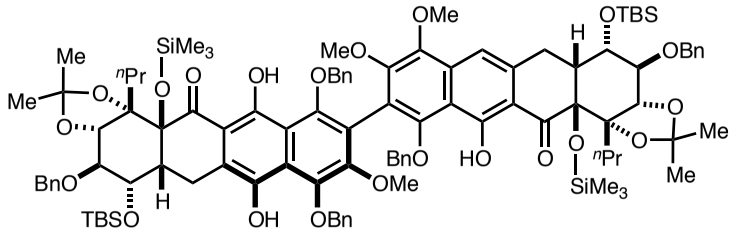
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
SPh
H
H
OTBS
OBn
O
O
Me
Me
BnO
HO
O
O
nPr
SiMe3
BnO
TBSO
H
OMe
OH
OBn

128b

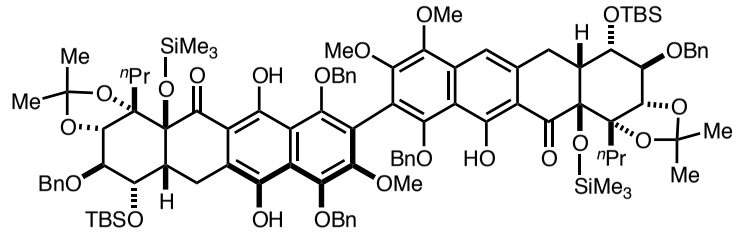
400

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
H
OTBS
OBn
O
Me
Me
O
O
nPr
SiMe3
BnO
HO
BnO
OMe
TBSO
H
OH
OBn

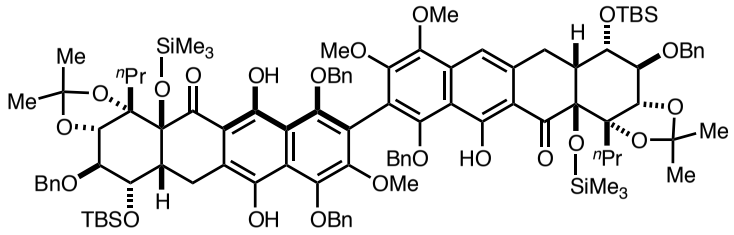
129a

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
H
OTBS
OBn
O
O
Me
Me
BnO
HO
O
O
nPr
SiMe3
BnO
TBSO
H
OMe
OH
OBn

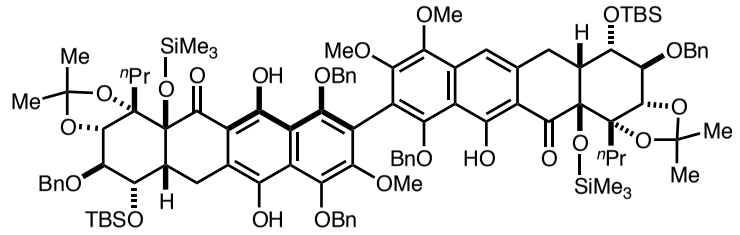
129a

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
H
OTBS
OBn
O
Me
Me
BnO
TBSO
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3

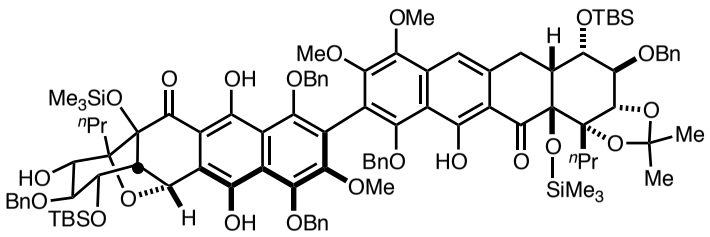
129b

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Me
Me
O
O
SiMe3
nPr
O
O
OH
OBn
MeO
OMe
H
OTBS
OBn
O
Me
Me
O
BnO
TBSO
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3

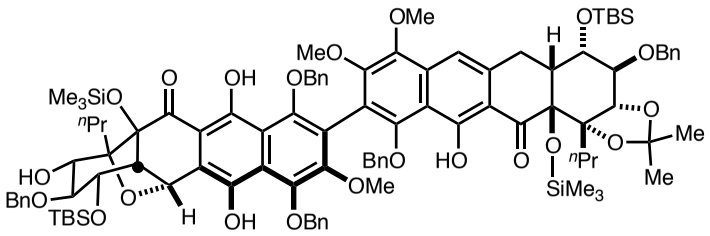
129b

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OMe
OTBS
H
MeO
OBn
Me3SiO
nPr
O
OH
OBn
O
Me
HO
BnO
TBSO
O
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3
Me

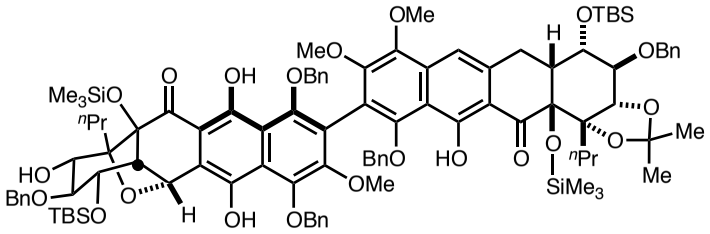
130a

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


OMe
OTBS
H
MeO
OBn
Me3SiO
nPr
O
OH
OBn
O
Me
HO
BnO
TBSO
O
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3
O
Me

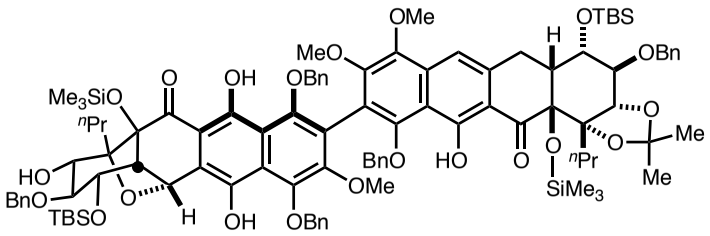
130a

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OMe
OTBS
H
MeO
OBn
Me3SiO
nPr
O
OH
OBn
O
Me
HO
BnO
TBSO
O
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3
O
Me

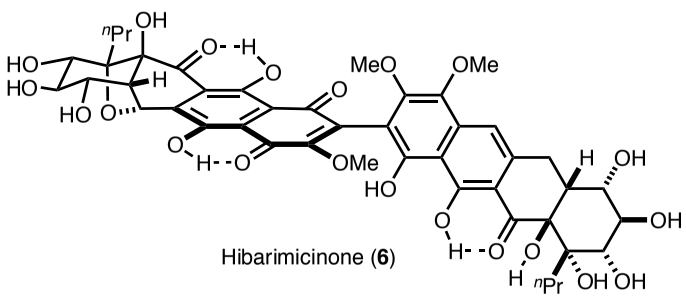
130b

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

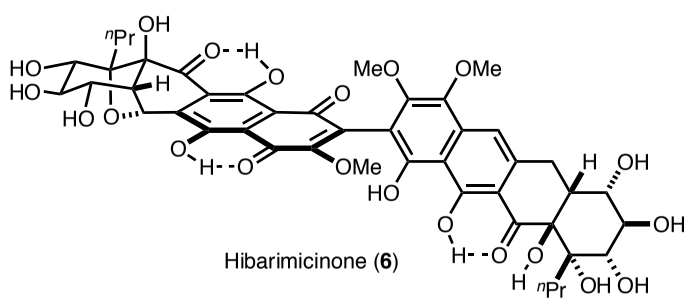

OMe
OTBS
H
MeO
OBn
Me3SiO
nPr
O
OH
OBn
O
Me
HO
BnO
TBSO
O
H
OH
OBn
OMe
BnO
HO
O
O
nPr
SiMe3
O
Me

130b

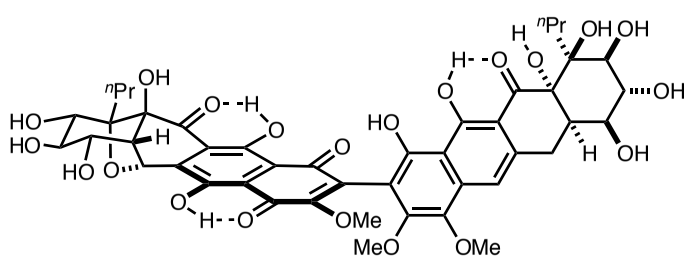
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



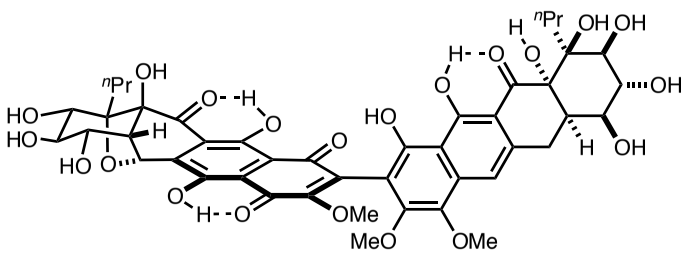
Hibarimicinone (**6**)



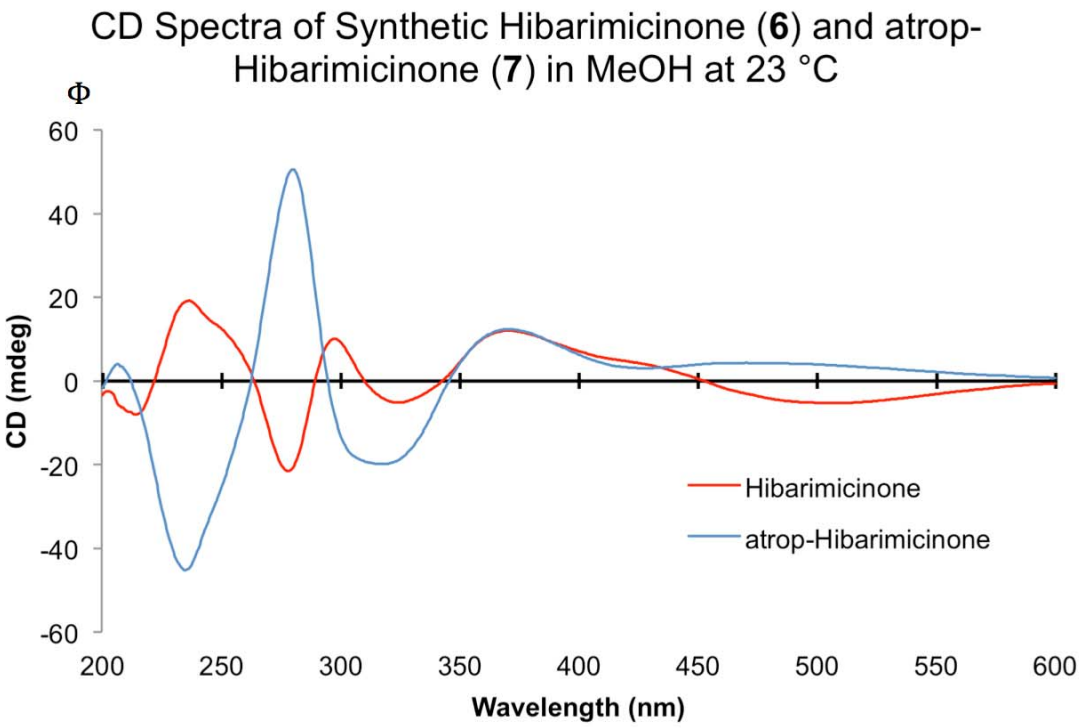
Hibarimicinone (**6**)

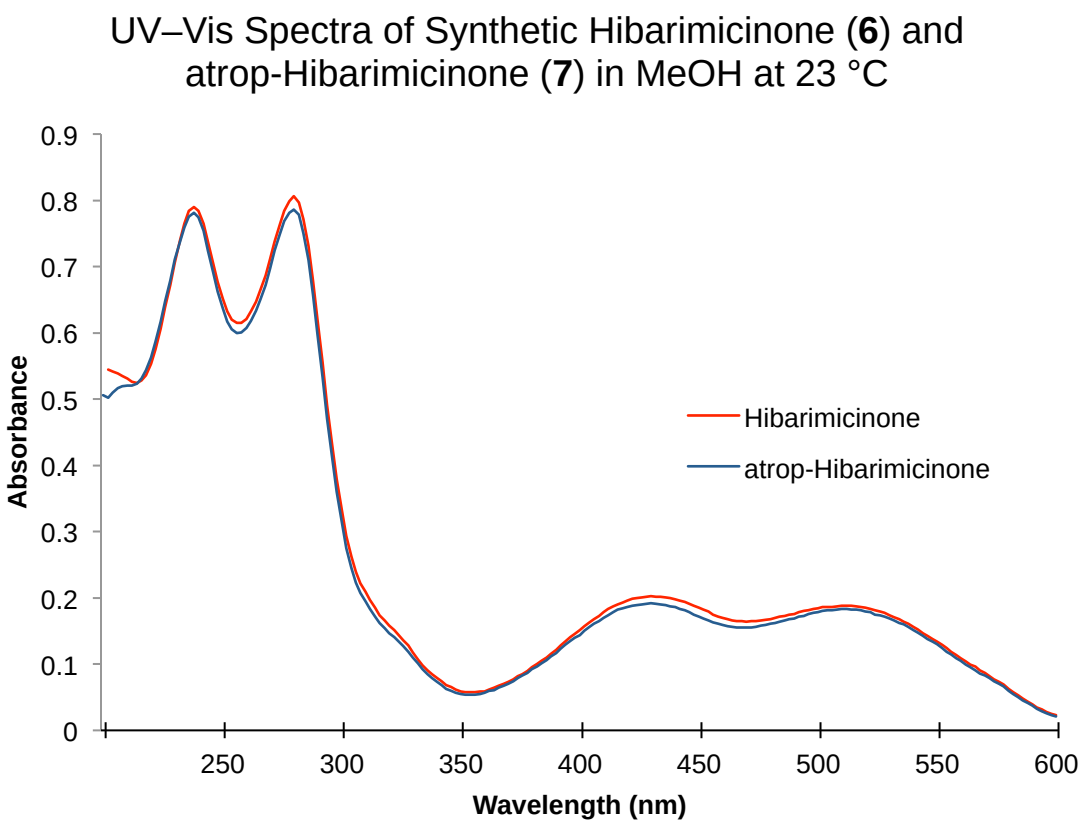


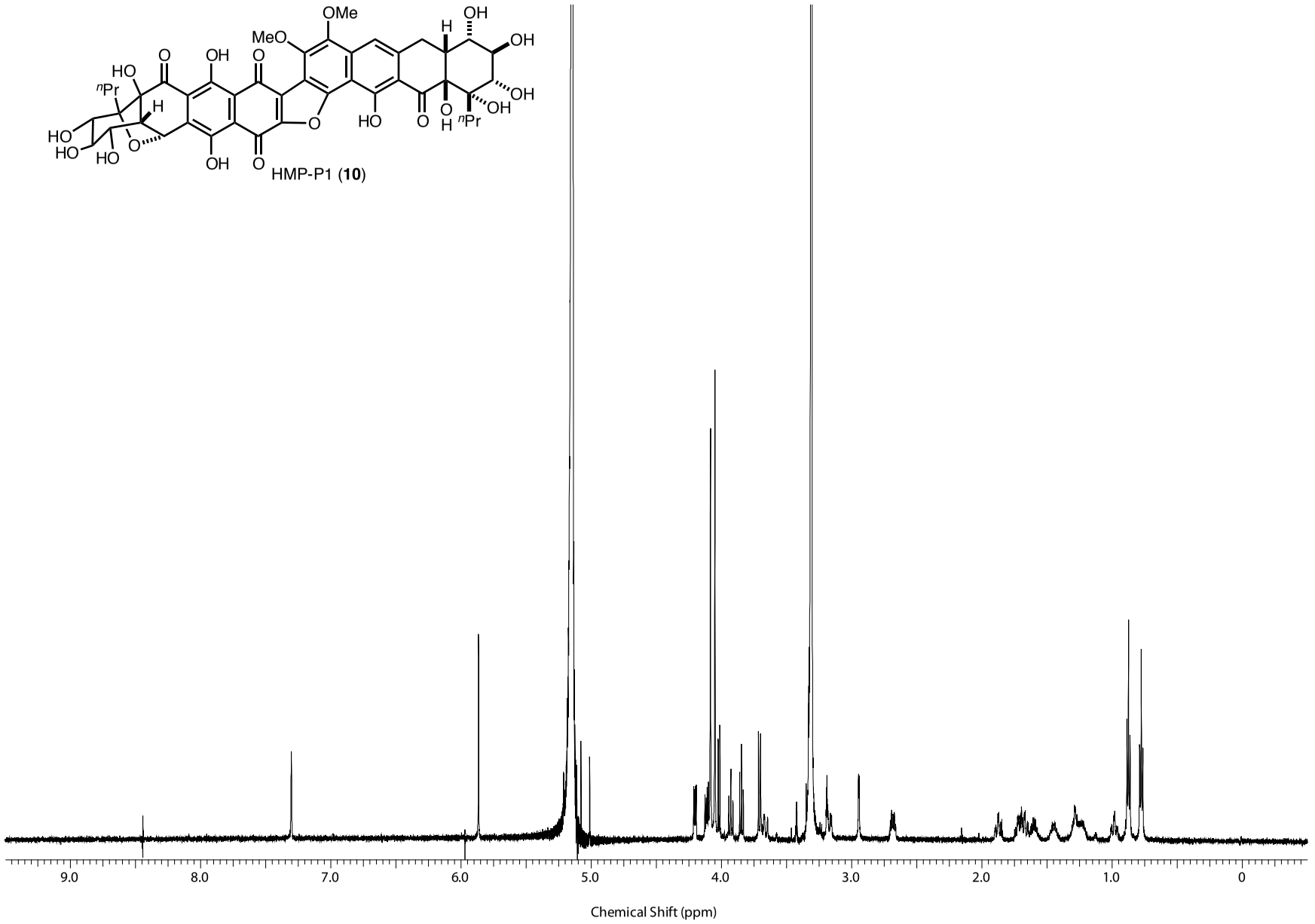
atrop-Hibarimicinone (**7**)

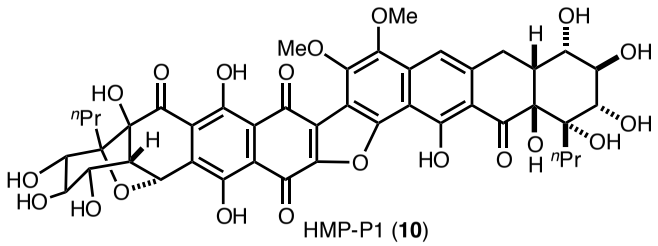


atrop-Hibarimicinone (**7**)


CD Spectra of Synthetic Hibarimicinone (6) and atrop-Hibarimicinone (7) in MeOH at 23 °C
Φ
60
40
20
0
-20
-40
-60
CD (mdeg)
200
250
300
350
400
450
500
550
600
Wavelength (nm)
Hibarimicinone
atrop-Hibarimicinone


UV–Vis Spectra of Synthetic Hibarimicinone (6) and atrop-Hibarimicinone (7) in MeOH at 23 °C
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Absorbance
250
300
350
400
450
500
550
600
Wavelength (nm)
Hibarimicinone
atrop-Hibarimicinone

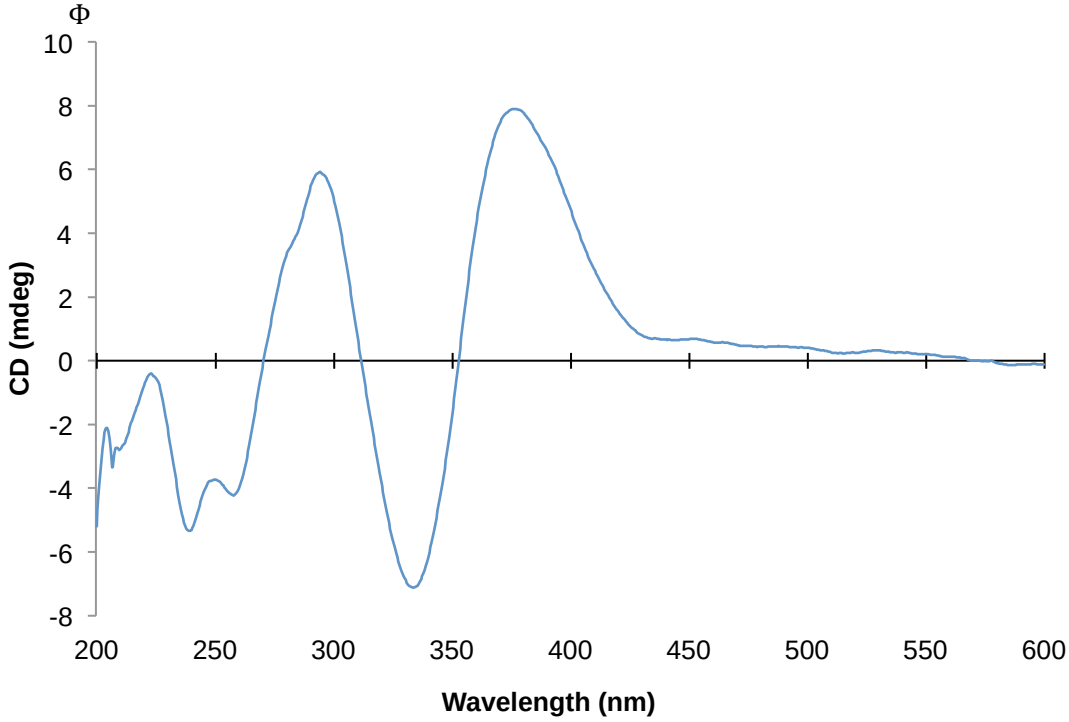

HMP-P1 (10)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


OMe
MeO
H
OH
OH
HO
O
OH
O
HO
nPr
H
OH
HO
HO
HO
O
O
HO
O
H
nPr
OH
O
OH

HMP-P1 (**10**)

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

CD Spectrum of Synthetic HMP-P1 (**10**)
in MeOH at 23 °C



UV–Vis Spectra of Synthetic HMP-P1 (**10**)
in MeOH at 23 °C